

Informing aetiologic research priorities for squamous cell oesophageal cancer in Africa: A review of setting-specific exposures to known and putative risk factors

V McCormack¹, D Menya², MO Munishi³, C Dzamalala^{4,5}, N Gasmelseed^{6,7}, M Leon Roux¹, M Assefa⁸, O Odipo⁹, M Watts¹⁰, AO Mwasamwaja^{3,12}, BT Mmbaga^{3,12}, G Murphy¹¹, CC Abnet¹¹, SM Dawsey¹¹, J Schüz¹

1 International Agency for Research on Cancer (IARC), Lyon, France.

2 Moi University, Eldoret, Kenya.

3 Kilimanjaro Clinical Research Institute, Moshi, Tanzania.

4 University of Malawi College of Medicine

5 Malawi Cancer Registry

6 National Cancer Institute University of Gezira, Sudan

7 Faculty of Science, University of Hafr Al Batin, Saudi Arabia

8 Radiotherapy Center, Addis-Ababa-University, Addis Ababa, Ethiopia.

9 University of Eldoret, Kenya

10 British Geological Survey

11 Division of Cancer Epidemiology and Genetics, National Cancer Institute, US

12 Kilimanjaro Christian Medical Centre, Moshi, Tanzania

Corresponding author: V. McCormack, Section of Environment and Radiation, IARC, 150 cours Albert Thomas, Lyon 08, CEDEX, France. Tel: +3347273 8566. Fax: +33 472738320. Email: mccormackv@iarc.fr

Keywords: Africa, oesophageal cancer, risk factors

Abbreviations

ASR	Age-standardized incidence rate (world population)
CI5	Cancer Incidence in Five Continents
EC	Oesophageal cancer (all histologies)
ESCC	Oesophageal squamous cell carcinoma
SLT	Smokeless tobacco

Abstract

Oesophageal squamous cell carcinoma (ESCC) is one of the most common cancers in most Eastern and Southern African countries, but its aetiology has been understudied to date. To inform its research agenda, we undertook a review to identify, of the ESCC risk factors that have been established or strongly suggested worldwide, those with a high prevalence or high exposure levels in any ESCC-affected African setting and the sources thereof. We found that for almost all ESCC risk factors known to date, including tobacco, alcohol, hot beverage consumption, nitrosamines and both inhaled and ingested PAHs, there is evidence of population groups with raised exposures, the sources of which vary greatly between cultures across the ESCC corridor. Research encompassing these risk factors is warranted and is likely to identify primary prevention strategies.

INTRODUCTION

Of all cancers, oesophageal cancer (EC), specifically oesophageal squamous cell carcinoma (ESCC), exhibits striking geographical variations in incidence rates, the highest being in the Asian ESCC belt. An African ESCC corridor also exists, stretching south from Sudan to the Eastern Cape Province of South Africa. Despite a mapping of this ESCC corridor by Burkitt, McGlashan *et al.* in 1960-70s (1;2), a corridor of this poor prognosis cancer remains today (3), in part because little aetiological research has hitherto been conducted. There are thus no unified hypotheses or evidence to explain this disease, thus a logical starting point for aetiological research is to evaluate whether ESCC risk factors, which have been established or strongly suggested throughout the world, are present in ESCC-affected African countries.

ESCC risk or protective factors include a range of lifestyle and environmental factors – low socioeconomic status, alcohol, tobacco, dietary factors (low fruit and vegetable intake and deficiencies in selenium and zinc), nitrosamines, opium use, consumption of hot beverages and exposures to polycyclic aromatic hydrocarbons (PAH) (4-14) and medical conditions and treatments including Lye disease, achalasia, Plummer-Vinson syndrome, Chaggas-associated mega-oesophagus, a history of certain head and neck cancers, and of therapeutic or repeated diagnostic radiation. Increased ESCC risk is also associated with a family history of this disease (4;15) and recent evidence suggests ESCC might be linked to poor oral health, animal contact and salty tea consumption (16-20).

With a view to informing the research agenda for ESCC in Africa to eventually inform primary prevention, we undertook to review its descriptive epidemiology, and to examine whether there is any evidence that established and suggested ESCC risk factors are prevalent or present at high exposure levels in ESCC-affected African populations.

METHODS

We summarized the descriptive epidemiology of ESCC in Africa, or of EC if histological types could not be distinguished, by geography, gender, age and time. We sourced national-level ESCC estimates from Arnold *et al.* who separated the 2012 IARC-GLOBOCAN EC burden into major histological types (21), and local estimates from Cancer Incidence in Five Continents (CI5) (22). We then searched for evidence or suggestions of either a high prevalence or high levels of exposure to ESCC risk factors across high incidence ESCC countries in Africa. High incidence countries were considered as those with at least 100 ESCC cases nationally in 2012 (both sexes) and for which the sex-specific ESCC age-standardised incidence rate (ASR, per 100,000) in either gender was higher than the corresponding world-average ASR of 7.7 (men) and 2.8 (women) (21). Twelve countries met these criteria, nine of which were in Eastern Africa

(Table 1). We did not include 20 of the 54 African countries for which GLOBOCAN incidence estimates were not based on data from the country itself (23).

Exposures examined are those that were identified as established or suggested ESCC risk factors in Kamangar et al.'s review (24), and, in addition, recently implicated factors mentioned in the Introduction. Evidence of setting-specific exposures were sourced from literature searches, and from co-authors' expert local knowledge as public health professionals, anthropologists and social scientists.

RESULTS

Descriptive epidemiology

Geographical variations

An estimated 27,503 people were diagnosed with EC in Africa in 2012, 25,278 (92%) of which were ESCC, and there were nearly as many EC deaths (25,244). Most patients are diagnosed with advanced disease, suffering from total dysphagia, thus palliative care is the primary therapy (25). The approximate anatomical distribution of tumours within the oesophagus is <20% in the upper third, 30-70% in the middle third and 20-50% in the lower third.

Figure 1 shows a map of national ESCC ASRs in men and women, demonstrating the steep geographical gradient. This trend is mirrored in higher-quality cancer registries in CI5, in which 4 populations from Africa have amongst the world's highest EC ASRs (Table 1), i.e. in Malawi, South Africa, Zimbabwe and Uganda. In terms of absolute numbers of cases, Tanzanian men and Ethiopian women additionally bear a large burden (Figure 2B). ASRs in men are exceeded by only 3 registries, all in China (Table 1). In West Africa, ASRs are over 20-fold lower despite the availability of similar diagnostic facilities for stomach cancers common to the region. However, precise delineation of the ESCC corridor is not possible due to the scarcity of high-quality cancer registry data and differential probabilities of under-diagnosis (26). Nevertheless, the broad geographical pattern is not dissimilar to McGlashan's 1969 hand-drawn map (2).

Malawi has Africa's highest ESCC ASR (26.5 and 19.8 in men and women, Figure 2A). In the capital Lilongwe, one quarter of all oesophago-gastroduodenoscopies are ESCC diagnoses and in Blantyre's CI5 registry, ESCC ranks second to Kaposi sarcoma (27;28). ESCC is also common in neighbouring Zambia and Zimbabwe (29;30) where an easterly bias in cases' origin does not appear to be an artefact of referral patterns as it was present within surgical patients alone (31). Excesses in northern Matabeleland of Zimbabwe and in north-east of Botswana were also reported in the 1960s and 70s (32;33). In Tanzania, Dar es Salaam and the northern regions of Arusha, Tanga and Kilimanjaro are known high incidence areas

(34). Continuing north, in 2012 Kenya bore Africa's second largest ESCC burden, particularly, but not exclusively, in the western highlands and rift-valley (31;35-38). ESCC is also reported in Kampala and Northern Uganda (39;40). Further north in Ethiopia, the highland Bale and Arsi zones of the Oromia region have raised incidence rates (41;42), whilst in Sudan, higher incidence areas in the north and in the south have both been documented (43;44).

Moving south, in South Africa's 2010 Cancer Registry Report, EC (all histologies) ranked the 3rd and 5th most common cancer in Black men and Black women respectively whilst it ranked much lower in other racial groups (45). This country's highest incidence areas are in the former Ciskei and Transkei areas within today's Eastern Cape Province and were the subject of early investigations by Rose, Burrell, Jaskiewicz, van Rensburg and others (46-48). There, ASRs of over 40 per 100,000 men and 20 in women occur in the Lusikisiki, Butterworth and Centane magisterial areas (49). These hotspots are somewhat removed geographically from the Eastern African hotspots, thus it is unclear whether they are a continuation or separate entity.

Gender, age, time trends

Contrasting to a very large excess in men in western lower-risk populations, overall 1.4 times as many men as women are diagnosed with ESCC in sub-Saharan African (21). As life expectancy is longer in women, there is a larger gender-gap (1.6:1) in ASRs (Figure 2C). In contrast, no male excess and possibly a female excess has been reported for Sudan and Ethiopia (50). It is unclear the extent to which gender-differentials in access to healthcare influences these ratios, e.g. a large male EC excess in the 1960s in Zimbabwe was suggested to be attributed undiagnosed elderly female cases from rural areas (51).

ESCC incidence rates increase steeply with age, thus an estimated 80% of EC cases (all histologies) in Eastern Africa occur in people aged 50 and over (23). At the same time, an apparently unique feature of the African burden is the consistent presence of extremely young EC patients (≤ 30 years) which, for example, constitute 8% of all cases in the Bomet district of West Kenya (37).

In the past half-century Africa has experienced urbanization, development, socio-political changes post-independence and in some parts the HIV epidemic. An accurate assessment of true incidence trends during this period is challenged by sparse data and by variations in the probability of cancer diagnosis (of all cancer types). In Kampala, Uganda, EC ASRs increased from 1960 to 1990, and thereafter have been constant to 2010 (52;53), similar to stable rates during 1991-2010 in Harare, Zimbabwe (29). In South Africa's Eastern Cape, significant declines (30% in men) in EC ASRs occurred between 2003-07 and 2008-12 (54), whilst in black gold miners rates were stable from the 1960s to 90s (55). Going further back in

time, in contrast to pre-biblical reports in other ESCC hotspots (e.g. Iran), early reports on cancer of any type are scarce in Africa. Nevertheless ESCC is documented in Kenya in 1935 (56) and in large numbers since the 1950s in Kenya (57) (58), South Africa (59-61) and a decade later in Tanzania and Botswana (33;34). However, during 1897-1956 in Mengo Hospital, Uganda, EC was not as common as it was further south (62). Oettlé suggests that ESCC was rare in South Africa (Johannesburg) prior to World War II and increased steeply thereafter, supported by systematic data on the large male mining populations (63).

Review of ESCC risk factors in EC-affected African settings

We now review established and putative ESCC risk factors in high-incidence ESCC African countries. A similar structure to that of Kamangar's review (24) is followed, with slight modifications to categories to include newly emerged factors. Table 2 lists the individual-level aetiologic studies that are referred to. These studies are case-control in design and with the exception of two South African studies and one Zimbabwean, each had less than 250 cases.

1. Habits

Tobacco: In South Africa, Malawi, Kenya, Uganda, Zambia and Zimbabwe, studies have found ESCC risk associated with tobacco smoking (cigarette or pipe), with odds ratios for smoking *versus* never smoking ranging from 2.6 to 8.0 (30;64-69). These ratios are notably larger than estimates from Asia. However, national-level prevalence of tobacco use is not high in most sub-Saharan African countries, and the average number of cigarettes smoked per day is low (70). Tobacco use exhibits a strong gender differential (prevalence <20% in men, <3% in women, see Table 3) - much larger than the corresponding differential in ESCC ASRs. However, national statistics mask strong socioeconomic gradients as illustrated by Demographic and Health Surveys (DHS) (71) across 30 sub-Saharan African countries in which tobacco prevalence was highest in poorer men (22% smoked, 7.8% used smokeless tobacco (SLT)) and in single men (35% smoked, 7.9% SLT), whilst women had lower prevalence but similar gradients. Types of tobacco used in ESCC-affected countries are listed in Table 3. East Africa is a tobacco-growing area, thus both traditional (possibly home-grown in rural areas) and commercial tobacco are used. In addition to cigarette and pipe smoking, SLT is chewed or used as nasal and oral snuff, and is culturally more acceptable than smoking in women (72). Oral snuff used in East Africa is highly alkaline due to the addition of salts (*magadi*) from certain rift valley lakes, increasing the pH and resulting in a higher free-base nicotine content than, for example, Swedish form snus (73). Levels of nicotine and tobacco-specific nitrosamines, particularly NNN and NNK, have been found to be particularly high in the African product (74).

Alcohol: Several African studies have suggested that alcohol consumption may be implicated in ESCC (31;64;66;69), but others found no association after adjustment, especially for tobacco use (65;67;75) (Table 2). Apart from small sample sizes, inconsistencies may be due to the range of ethanol content, constituents, contaminants and types of home-brews and home-distillations consumed. Although alcohol consumption per capita is low, amongst drinkers, average consumption is higher than in Europe and the Americas and binge drinking is common (76). Consumption is higher in men than women (e.g. in Kenya, 31% of men are drinkers, 13% of women), 50-60% of drinkers get drunk frequently (77) and drinking can start early in life (78). Lower alcohol consumption in men in Sudan and Ethiopia may explain the apparent absence of a male excess.

Some commonly consumed alcohols and their local varieties are listed in Table 3. They include high ethanol-content alcohols, as were implicated early on by Burrell and McGlashan, particularly *kachasu* in Zambia and Malawi and *cidiviki* in the Eastern Cape (2;79). Other common spirits distilled from maize, millet and sorghum, are *chang'aa* in Kenya, *gongo* in Tanzania (literally “kill me quick”) and aräqe in Ethiopia which are 18-54% ethanol (77;80). When made with maize cobs, a high methanol content is often present and can cause temporary blindness. In recent decades, distillations may be adulterated for an additional kick with chemicals (e.g. petrol or pesticides) and at 10-20% of the cost of commercial alcohols, these spirits remain an attractive option for the poor and, despite being illicit brews, can be obtained without too much difficulty. The extent of abuse was hinted by Burrell, who observed hypopigmentation of the lips in ESCC patients, similar to that in shebeen queens (79). Commercial spirits are also consumed and in the past 2 decades many East African countries have experienced steep rises in their consumption in the form of individually sold plastic sachets (30/50/100 ml) and small bottles. The small sachets, known as blackberries, *tujilijili* and *viroba* in Malawi, Zambia and Tanzania respectively, are easily concealed, can be drunk throughout the day, purchased with little money, and are also consumed by the youth. The extent of the abuse in Zambia, which necessitated the established of treatment centres for young men with this addiction, led to the ban on their production in 2012.

Concerning lower ethanol content alcohols, in addition to commercial drinks (mostly beer), home brews (2-5% ethanol) are consumed in very large volumes (serving sizes 1 to 2 litres), such as *busaa* (finger millet malt) or *mbege* and *muratina* (sugar cane and sausage-tree fruit) and the commercial *chibuku* in Malawi (sorghum-based). In addition to ethanol and acetaldehyde, other carcinogenic contaminants may be present in moonshines – for example residues from old oil drums used to prepare distillations and petrol or diesel jerrycans used for storage.

Opium – Opium is associated with ESCC risk in Iran (81), but in Africa, although opium was first cultivated in the 19th century, its production was short lived, and thus traditional opium use is not known in the continent.

Drinking mate – This drink is not consumed in Africa.

Hot beverages and foods: Several observations point towards the contribution of hot beverages. A South African study showed increased ESCC risk associated with daily tea consumption, though temperatures were not measured (82). Further, hot beverage consumption is prevalent in the Kilimanjaro region of Tanzania where the average temperature at first sip was 71°C, which correlated with a self-reported history of tongue burning (83). These tea temperatures far exceeded those in Iran where a strong tea temperature-ESCC association was observed (odds ratio 8 for very hot vs. warm/lukewarm tea) (84). In the Tanzanian study, consumption of milky tea was particularly hot, as it cooled slower than black tea. In the preparation of milky tea, unpasteurized milk with a high fat content (which retains more heat than water alone) is boiled together with tea and water and tea is served directly from hot coals or from a thermal flask. Sugar is also often added. This method of tea preparation is also common to neighbouring Kenya and Malawi, and in all of these countries, hot beverages heat the body during cold mornings or evenings at higher altitudes. In an Ethiopian ESCC case-only series, the majority of patients had consumed hot porridge (*genfo*, usually made from barley) and/or hot coffee (85). Some cultures report consumption of hot soup the morning after a night of drinking. Consumption of hot maize as a contributor to ESCC in the Eastern Cape was also suggested by Burrell in 1957; oral heat tolerance tests demonstrated raised tolerances in ESCC patients (69-75°C) but not in the general community (53-62°C) (79). Other common hot food and beverage consumption is listed in Table 3.

Pickled foods – Pickling is not a common method of food preservation in the African ESCC corridor, other than in some culinary items in South Africa, where Sewram *et al.* found no association with ESCC (86). Salted foods are mentioned in section 7.

2. Diet: Nutritional deficiencies and food contaminants

In the fertile sub-tropical rural areas of East Africa, subsistence farming is common, and a wide variety of seasonal fruits and vegetables are grown and consumed (87). The staple food shifted from sorghum to maize over the last century, which is typically consumed daily in ground form alongside a dish of beans and green leafy vegetables (kale, spinach and others). Associated with this pattern of food consumption are two strong dependencies, namely a heavy reliance on maize for a large proportion of calorie intake and a heavy reliance on locally-sourced foods. In South Africa, two earlier studies found

increased risks associated with increasing consumption of purchased maize (82) or maize (home grown or commercial not specified) (88), whilst more recent findings were null (86). Proposed, but unproven, mechanisms for a maize-associated ESCC risk are: (i) Because maize is not cooked by nixtamalization in Africa (an alkaline cooking method which increases nutrient availability), it has low levels of available niacin (vitamin B₃), and niacin deficiency resulting in pellagra disease is associated with an increased risk of ESCC. On the other hand, commercial maize meal in South Africa has been fortified with nicotinic acid since 2003, and persons who consume maize often consume it with nicotinic rich legumes. (ii) Maize may be contaminated with the mycotoxin fumonisin, a hypothesized (but not proven) carcinogen. (iii) Silica contamination of home-ground maize may irritate the oesophageal mucosa causing chronic inflammation (89).

Concerning the dependency on locally-sourced diets, if deficiencies in ESCC-implicated nutrients or excess of harmful constituents are present in crops and cereals, then persons whose diets derive almost exclusively from those crops will themselves be prone to deficiencies/excesses. Further, if crop contents are under geochemical control, it may explain the peculiar geographical distribution proximal to the rift valley and highland areas of Eastern Africa. Several related observations are noteworthy. In Africa's highest ESCC-incidence country, Malawi, severe primary selenium deficiency is prevalent because of reduced soil-to-crop selenium transfers in acidic soils (90). On a larger scale, an ecological analysis found that national-level risks of selenium and zinc deficiency are more common in Africa's high-incidence ESCC countries (91). Further, the traditional practice of adding *magadi* soda or bean debris ash in food preparation – for taste and to speed up cooking - has been shown to reduce bioavailable zinc and iron in staples (92).

Iron-deficiencies result in geophagia in much of the ESCC corridor, especially during pregnancy. This practice may be an exposure marker for iron deficiency, or to physical damage or silica exposure, but whether these are related to ESCC is unknown. Food sources of PAHs and nitrosamines are discussed in section 5 (chemical carcinogens).

3. Medications and predisposing conditions

We are not aware of any reports suggesting that Lye, Chaggas-associated mega-oesophagus or achalasia are common in the African ESCC-corridor. Plummer-Vinson syndrome is not reported, but of its symptoms of oesophageal webs, chronic iron-deficiency anaemia and koilonychia (spoon fingernails), co-authors clinical experience verify that the latter two occur in East Africa.

Family history of ESCC and genetic susceptibility need to be evaluated in Africa; but study designs and questions need to consider that polygamy is prevalent in some of the ESCC-affected east African populations, thus the total number of siblings may be large and maternal and paternal lineage complex.

4. Infections

HPV and cervical cancer is prevalent in much of the ESCC corridor, but a large international study found no overall association of ESCC with common HPV types with ESCC (24;93). Regarding other infections, whilst HIV prevalence is high in several ESCC-affected countries and HIV-positive patients commonly experience oesophageal candidiasis, evidence from Africa and worldwide suggests that ESCC is not a HIV-associated malignancy worldwide (93;94). Further, time trends in ESCC incidence rates in most HIV-affected settings have been stable during the HIV epidemic. Nevertheless, a review in Malawi has noted concomitant increases in Kaposi sarcoma and ESCC incidence rates (95), and a Zambian study reported a HIV-ESCC link (30). Another infection, *Schistosoma mansoni*, also affects parts of the ESCC corridor, particularly fishing communities, and endoscopy clinics diagnosing ESCC patients also see patients with *S. mansoni*-associated oesophageal varices. However no link between this parasite and ESCC is suggested; in Moshi, North Tanzania, patients with schistosomiasis oesophageal varices originate from the southern low-lying rice growing area, and ESCC patients from the base of Mount Kilimanjaro.

5. Chemical Carcinogens

PAH (a group of chemicals arising from partial combustion of organic matter) may be implicated in ESCC in East Africa, primarily due to biomass burning for fuel. In the poorer communities affected by ESCC, wood, charcoal, dung and maize cobs are the primary fuel source. Fires for cooking are often kept smouldering continuously for hours and in the colder high altitude areas are also needed for heating. Household air pollution studies using measured continuous monitoring have shown average daily PM10 concentrations of 2800 to 5000 mg/m³ in young and adult women in Kenya, which were 2.5 to 5 times higher than that of their male counterparts (96). Women had particularly high exposures, owing to brief high-intensity exposures during cooking in small kitchen rooms, often without any form of ventilation. Further, in some cultures, young children, adolescent girls, menstruating women and grandmothers sleep all night in the safe and private kitchen beside a smouldering fire. In Sudan, PAH inhalation may also be associated with use of the *dukhan* by married women, a tradition of bathing the full face over fumes of an acacia burner. Suffering from watery eyes at the fireside has been used as an exposure marker and has been linked to ESCC risk (30;97).

In terms of ingested PAHs, apart from occasionally consumed barbecued foods, in Kenya a traditional Kalenjin fermented milk *mursik* is flavoured by crushing a burning/burnt acacia stick in the milk and thus will have extremely high PAH levels (98). It also contains acetaldehyde (99), which may also be present in other fermented/soured milks consumed in East Africa. In North Tanzania, there is the habit, though less common today, of chewing charcoal (*makaa*) to whiten teeth in this fluorosis-affected area.

Concerning nitrosamines, apart from those in tobacco and beer, prevalent exposure sources are smoked fish, which are commonly consumed near the salt water lakes of the rift valley, whilst cured meats and bacon are rarely consumed in this region. Another less studied potential source of nitrosamines in much of East Africa are green leafy vegetables (*mchicha* in Tanzania, *imifino* South Africa) which are consumed alongside maize meal almost on a daily basis throughout life. The mixture of (wild) leafy vegetables depends on local availability, but commonly includes kale (*sukuma wiki*), spinach, *Solanum nigrum* (black nightshade, *mnavu/mnafu* in Tanzania), amaranth and Chinese cabbage. High nitrate levels in some of these vegetables, particularly in spinach, amaranth and black nightshade, may lead to N-nitrosamine production (100). Two South African studies have reported increased ESCC risks associated with their consumption alone (88) or analysed as part of a maize-imifino-beans type dietary pattern (86).

6. Occupational exposures

In Southern Africa's more industrialized economy, Vizcaino et al reported higher ESCC risk associated with being a miner (odds ratio 2.5) or being in a low occupational status (odds ratio 1.5) compared to being in medium or high status jobs. As farming, including small-scale farming and larger-scale tea and coffee plantations, is the major occupation in most of the affected rural population, pesticide exposures may also be relevant, e.g. from DDT used on coffee trees in the past, and diazinon.

7. Other setting, cultural and poverty-associated indicators

Personal and cultural habits

Other potentially relevant setting-specific habits which may cause damage to the oesophageal mucosa are self-induced vomiting (akin to ESCC risks associated with bulimia nervosa in the west) which is a common cultural practice (~80% prevalence) in the Eastern Cape areas of South Africa (101). Poor oral health may also be relevant, as reported in Kenya (69). Further, of unknown relevance, in the ESCC hotspots in West Kenya and Kilimanjaro, dental fluorosis is endemic, due to high fluoride levels in water or from *magadi* salt (trona) used for tenderizing food (102;103). Salty foods are also common, particularly

those sourced from the saltwater rift valley lakes. Oral health and ESCC risk may also be influenced by the common habit of *khat (Qat)* chewing in the northern parts of the EC corridor.

Living environment

In the poorer rural populations affected by ESCC, the living environment is often in close proximity to animals, water supplies can be untreated and biomass is the main fuel (discussed in part 5). Water sources include boreholes, dams, wells and streams, and are often untreated or have little filtration. In urban slums of ESCC-affected West Kenya, well water can have nitrate levels that exceed safe limits. Goats, chickens and cows are kept close to human's living areas, thus recent observations of raised risks associated with life-long ruminant contact need investigating. Finally, of unknown relevance for ESCC in humans, in 1971 Plowright reported a peculiar high incidence of rumenal cancer in cattle in Kenya's Narok district which neighbours today's human hotspot in Bomet district. The cancers occurred during a dry season when cattle were forced to graze on higher grounds (104). The cancers were postulated to be related to excess nitrate intake in molybdenum-deficient plants or to ptaquiloside-containing bracken fern (*ptaquiloside aquilinum*), which is suggested to cause bladder and possibly rumenal cancers in animals.

DISCUSSION

This review of ESCC risk factors in the African ESCC corridor adopted a broad perspective, building on the observation that in most high-risk settings, multiple carcinogens are co-present and cancer arises after chronic exposures. We focused on local sources of exposures, as it has previously been emphasized that the same agent, such as PAH (in smoke, mate or *mursik*), alcohol, and tobacco, may differ across settings. Exposure-source heterogeneity is likely to be particularly pronounced in Africa, driven by distinct local cultures and customs of the multiple ethnic groups, as well as a strong influence of the local physical environment on the staple diet, fuel and water sources.

The descriptive epidemiology and the analytical epidemiologic evidence-base, albeit limited, provide several initial clues to aetiology. Extreme, up to 20-fold differences, in incidence rates between the ESCC corridor and other parts of sub-Saharan Africa cannot be explained by health care access or cancer registration differences. A male excess in most countries is likely to be real and would point to likely gender-patterned exposures. Additionally, extremely young cases may indicate a genetic predisposition and/or exposures present and acting from very early in life to accumulate sufficient genetic damage within 2-3 decades. The lack of significant temporal increases in the past 3-4 decades suggest

that dominant factors underlying the corridor have not been recently introduced to this setting, but must have been present since the 1950s, if not before.

Aetiologic research priorities for ESCC in Africa thus need to take these observations into perspective, in particular the peculiar geographical distribution, young cases and male excess. However, without any obvious greater degree of cultural, lifestyle or genetic similarities specific to the corridor, the presence of another dominant factor(s) is/are likely, acting in synergy with multiple other factors. The latter factors worth investigation include high-ethanol alcohols, tobacco, hot beverages, dietary deficiencies, PAH via indoor air pollution and ingestion, nitrosamines, animal contact and the role of salt intakes. Whilst at first glance many of these exposures are by no means unique to this belt, the same holds true for the ESCC belt in Asia and clues may be provided by examining setting-specific sources, use, age at exposure, and combinations of exposures, to disentangle what may be most unique to the ESCC corridor. For example, for tobacco, relative risk estimates from Africa appear to be higher than from Asia, but may be acting in synergism with other chronic exposures, such as PAH, thermal injury or alcohol.

The research agenda thus needs to cast a wide net to encompass new hypotheses, alongside inclusion of the above-mentioned factors. Given the large diversity in genomes across the expanse of the ESCC corridor, this missing factor is likely to be environmental and not primarily high-penetrance genetic traits; nevertheless genetic susceptibility studies are still warranted, as common low-penetrance mutations may contribute to individual risk alone or in combination with environmental agents.

Research attention to inform strategies to reduce avoidable ESCC cancer deaths in this African corridor, one of the world's most pronounced localized areas of any cancer, is long overdue. Early disease detection is a possibility in extremely high-risk settings such as in the Chinese hotspots where ASRs are over 4-fold higher than other high-risk areas, and in Africa such high-risk subpopulations still need to be identified prior to any possible implementation. For primary prevention strategies, on a positive note, many of the suggested aetiologic factors are modifiable and, if altered appropriately, would prevent many cases of this very fatal cancer. Notably, in addition, they would have major beneficial effects on multiple NCDs. Risk reduction strategies would include cessation of tobacco use, reducing alcohol intakes, promotion of clean cooking stoves and ventilation in cooking and sleeping areas, drinking hot beverages at lower temperatures, and bio-fortification to improve crop nutrient levels. However, identification and prioritising of prevention strategies first needs a robust evidence-base generated from within the African ESCC corridor, and this will require a multi-centre multi-country coordinated research effort to produce definitive results.

Funding: IARC

Conflict of interest: The authors declare that they have no conflict of interest.

Reference List

- (1) Hutt MS, Burkitt D. Geographical distribution of cancer in East Africa: a new clinicopathological approach. *Br Med J* 1965 Sep 25;2(5464):719-22.
- (2) McGlashan ND. Oesophageal cancer and alcoholic spirits in central Africa. *Gut* 1969 Aug;10(8):643-50.
- (3) Cheng ML, Zhang L, Borok M, Chokunonga E, Dzamamala C, Korir A, Wabinga HR, Hiatt RA, Parkin DM, Van LK. The incidence of oesophageal cancer in Eastern Africa: identification of a new geographic hot spot? *Cancer Epidemiol* 2015 Apr;39(2):143-9.
- (4) Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, Mark SD, Qiao YL, Taylor PR. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer* 2005 Jan 20;113(3):456-63.
- (5) Islami F, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Abedi-Ardekani B, Merat S, Nasseri-Moghaddam S, Semnani S, Sepehr A, Wakefield J, Moller H, et al. Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. *Int J Epidemiol* 2009 Aug;38(4):978-88.
- (6) Kamangar F, Strickland PT, Pourshams A, Malekzadeh R, Boffetta P, Roth MJ, Abnet CC, Saadatian-Elahi M, Rakhshani N, Brennan P, Etemadi A, Dawsey SM. High exposure to polycyclic aromatic hydrocarbons may contribute to high risk of esophageal cancer in northeastern Iran. *Anticancer Res* 2005 Jan;25(1B):425-8.
- (7) Jakszyn P, Gonzalez CA. Nitrosamine and related food intake and gastric and oesophageal cancer risk: a systematic review of the epidemiological evidence. *World J Gastroenterol* 2006 Jul 21;12(27):4296-303.
- (8) Bartsch H, Spiegelhalter B. Environmental exposure to N-nitroso compounds (NNOC) and precursors: an overview. *Eur J Cancer Prev* 1996 Sep;5 Suppl 1:11-7.
- (9) Deziel NC, Wei WQ, Abnet CC, Qiao YL, Sunderland D, Ren JS, Schantz MM, Zhang Y, Strickland PT, Abubaker S, Dawsey SM, Friesen MC, et al. A multi-day environmental study of polycyclic aromatic hydrocarbon exposure in a high-risk region for esophageal cancer in China. *J Expo Sci Environ Epidemiol* 2013 Jan;23(1):52-9.
- (10) Abedi-Ardekani B, Kamangar F, Hewitt SM, Hainaut P, Sotoudeh M, Abnet CC, Taylor PR, Boffetta P, Malekzadeh R, Dawsey SM. Polycyclic aromatic hydrocarbon exposure in oesophageal tissue and risk of oesophageal squamous cell carcinoma in north-eastern Iran. *Gut* 2010 Sep;59(9):1178-83.
- (11) Vioque J, Barber X, Bolumar F, Porta M, Santibanez M, de la Hera MG, Moreno-Osset E. Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain. *BMC Cancer* 2008;8:221.

- (12) Abnet CC, Lai B, Qiao YL, Vogt S, Luo XM, Taylor PR, Dong ZW, Mark SD, Dawsey SM. Zinc concentration in esophageal biopsy specimens measured by x-ray fluorescence and esophageal cancer risk. *J Natl Cancer Inst* 2005 Feb 16;97(4):301-6.
- (13) Mark SD, Qiao YL, Dawsey SM, Wu YP, Katki H, Gunter EW, Fraumeni JF, Jr., Blot WJ, Dong ZW, Taylor PR. Prospective study of serum selenium levels and incident esophageal and gastric cancers. *J Natl Cancer Inst* 2000 Nov 1;92(21):1753-63.
- (14) Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, Johnson LL, Gail MH, Dong ZW, Yu B, Mark SD, Taylor PR. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. *J Natl Cancer Inst* 2009 Apr 1;101(7):507-18.
- (15) Bhat GA, Shah IA, Makhdoomi MA, Iqbal B, Rafiq R, Nabi S, Masood A, Lone MM, Dar NA. CYP1A1 and CYP2E1 genotypes and risk of esophageal squamous cell carcinoma in a high-incidence region, Kashmir. *Tumour Biol* 2014 Jun;35(6):5323-30.
- (16) Abnet CC, Kamangar F, Islami F, Nasrollahzadeh D, Brennan P, Aghcheli K, Merat S, Pourshams A, Marjani HA, Ebadati A, Sotoudeh M, Boffetta P, et al. Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2008 Nov;17(11):3062-8.
- (17) Dar NA, Islami F, Bhat GA, Shah IA, Makhdoomi MA, Iqbal B, Rafiq R, Lone MM, Abnet CC, Boffetta P. Poor oral hygiene and risk of esophageal squamous cell carcinoma in Kashmir. *Br J Cancer* 2013 Sep 3;109(5):1367-72.
- (18) Dar NA, Islami F, Bhat GA, Shah IA, Makhdoomi MA, Iqbal B, Rafiq R, Lone MM, Boffetta P. Contact with animals and risk of oesophageal squamous cell carcinoma: outcome of a case-control study from Kashmir, a high-risk region. *Occup Environ Med* 2014 Mar;71(3):208-14.
- (19) Dar NA, Bhat GA, Shah IA, Iqbal B, Rafiq R, Nabi S, Lone MM, Islami F, Boffetta P. Salt tea consumption and esophageal cancer: a possible role of alkaline beverages in esophageal carcinogenesis. *Int J Cancer* 2015 Mar 15;136(6):E704-E710.
- (20) Nasrollahzadeh D, Ye W, Shakeri R, Sotoudeh M, Merat S, Kamangar F, Abnet CC, Islami F, Boffetta P, Dawsey SM, Brennan P, Malekzadeh R. Contact with ruminants is associated with esophageal squamous cell carcinoma risk. *Int J Cancer* 2015 Mar 15;136(6):1468-74.
- (21) Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 2015 Jan 1;64(381):387.
- (22) Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Pineros M, Steliarova-Foucher E, Swaminathan R, Ferlay J. *Cancer Incidence in Five Continents.*, 2013 ed 2014.
- (23) Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015 Mar 1;136(5):E359-E386.

- (24) Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. *Gastroenterol Clin North Am* 2009 Mar;38(1):27-57.
- (25) Parker RK, White RE, Topazian M, Chepkwony R, Dawsey S, Enders F. Stents for proximal esophageal cancer: a case-control study. *Gastrointest Endosc* 2011 Jun;73(6):1098-105.
- (26) Duron V, Bii J, Mutai R, Ngetich J, Harrington D, Parker R, White R. Esophageal cancer awareness in Bomet district, Kenya. *Afr Health Sci* 2013 Mar;13(1):122-8.
- (27) Msyamboza KP, Dzamalala C, Mdokwe C, Kamiza S, Lemerani M, Dzowela T, Kathyola D. Burden of cancer in Malawi; common types, incidence and trends: national population-based cancer registry. *BMC Res Notes* 2012;5:149.
- (28) Wolf LL, Ibrahim R, Miao C, Muyco A, Hosseinipour MC, Shores C. Esophagogastroduodenoscopy in a public referral hospital in Lilongwe, Malawi: spectrum of disease and associated risk factors. *World J Surg* 2012 May;36(5):1074-82.
- (29) Chokunonga E, Borok MZ, Chirenje ZM, Nyakabau AM, Parkin DM. Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991-2010. *Int J Cancer* 2013 Aug 1;133(3):721-9.
- (30) Kayamba V, Bateman AC, Asombang AW, Shibemba A, Zyambo K, Banda T, Soko R, Kelly P. 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* 2015 Apr;4(4):588-95.
- (31) Wapnick S, Zanamwe LN, Chitiyo M, Mynors JM. Cancer of the esophagus in Central Africa. *Chest* 1972 Jun;61(7):649-54.
- (32) Parkin DM, Vizcaino AP, Skinner ME, Ndhlovu A. Cancer patterns and risk factors in the African population of southwestern Zimbabwe, 1963-1977. *Cancer Epidemiol Biomarkers Prev* 1994 Oct;3(7):537-47.
- (33) Macrae SM, Cook BV. A retrospective study of the cancer patterns among hospital in-patients in Botswana 1960-72. *Br J Cancer* 1975 Jul;32(1):121-33.
- (34) Hiza PR. Malignant disease in Tanzania. *East Afr Med J* 1976 Feb;53(2):82-95.
- (35) White RE, Abnet CC, Mungatana CK, Dawsey SM. Oesophageal cancer: a common malignancy in young people of Bomet District, Kenya. *Lancet* 2002;360(9331):462-3.
- (36) Wakhisi J, Patel K, Buziba N, Rotich J. Esophageal cancer in north rift valley of Western Kenya. *Afr Health Sci* 2005 Jun;5(2):157-63.
- (37) Parker RK, Dawsey SM, Abnet CC, White RE. Frequent occurrence of esophageal cancer in young people in western Kenya. *Dis Esophagus* 2010 Feb;23(2):128-35.

- (38) Dawsey SP, Tonui S, Parker RK, Fitzwater JW, Dawsey SM, White RE, Abnet CC. Esophageal cancer in young people: a case series of 109 cases and review of the literature. *PLoS One* 2010;5(11):e14080.
- (39) Parkin DM, Nambooz S, Wabwire-Mangen F, Wabinga HR. Changing cancer incidence in Kampala, Uganda, 1991-2006. *Int J Cancer* 2010 Mar 1;126(5):1187-95.
- (40) Alema ON, Iva B. Cancer of the esophagus: histopathological sub-types in northern Uganda. *Afr Health Sci* 2014 Mar;14(1):17-21.
- (41) Bane A, Ashenafi S, Kassa E. Pattern of upper gastrointestinal tumors at Tikur Anbessa Teaching Hospital in Addis Ababa, Ethiopia: a ten-year review. *Ethiop Med J* 2009 Jan;47(1):33-8.
- (42) Ahmed AA. The surgical management and outcome of oesophageal cancer in Addis Ababa. *Ethiop Med J* 2000 Jul;38(3):147-52.
- (43) Gasmelseed N, Abudris D, Elhaj A, Eltayeb EA, Elmadani A, Elhassan MM, Mohammed K, Elgaili EM, Elbalal M, Schuz J, Leon ME. Patterns of Esophageal Cancer in the National Cancer Institute at the University of Gezira, in Gezira State, Sudan, in 1999-2012. *Asian Pac J Cancer Prev* 2015;16(15):6481-90.
- (44) Boulos PB, El Masri SH. Carcinoma of the oesophagus in the Sudan. *Trop Geogr Med* 1977 Jun;29(2):150-4.
- (45) http://www.nioh.ac.za/assets/files/NCR_Final_2010_tables%281%29.pdf. South African National Cancer Registry 2010. 2016.
- (46) Rose EF. A study of esophageal cancer in the Transkei. *Natl Cancer Inst Monogr* 1967 Jul;25:83-96.
- (47) Jaskiewicz K, Marasas WF, van der Walt FE. Oesophageal and other main cancer patterns in four districts of Transkei, 1981-1984. *S Afr Med J* 1987 Jul 4;72(1):27-30.
- (48) BURRELL RJ. Distribution maps of esophageal cancer among Bantu in the Transkei. *J Natl Cancer Inst* 1969 Oct;43(4):877-89.
- (49) Somdyala NI, Bradshaw D, Gelderblom W. Eastern Cape Province Cancer Registry Technical Report. 2013 Aug 1.
- (50) Mohammed ME, Abuidris DO, Elgaili EM, Gasmelseed N. Predominance of females with oesophageal cancer in Gezira, Central Sudan. *Arab J Gastroenterol* 2012 Dec;13(4):174-7.
- (51) Skinner ME. 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* 1967 Jul;25:57-71.
- (52) Wabinga HR, Nambooz S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991-2010. *Int J Cancer* 2014 Jul 15;135(2):432-9.

- (53) Wabinga HR, Parkin DM, Wabwire-Mangen F, Nambooz S. Trends in cancer incidence in Kyadondo County, Uganda, 1960-1997. *Br J Cancer* 2000 May;82(9):1585-92.
- (54) Somdyala NI, Parkin DM, Sithole N, Bradshaw D. Trends in cancer incidence in rural Eastern Cape Province; South Africa, 1998-2012. *Int J Cancer* 2014 Sep 18.
- (55) McGlashan ND, Harington JS, Chelkowska E. Changes in the geographical and temporal patterns of cancer incidence among black gold miners working in South Africa, 1964-1996. *Br J Cancer* 2003 May 6;88(9):1361-9.
- (56) Vint FW. *Malignant Disease in the Natives of Kenya.*, 226 ed 1935. p. 628-30.
- (57) Linsell CA. Cancer incidence in Kenya 1957-63. *Br J Cancer* 1967 Sep;21(3):465-73.
- (58) Gatei DG, Odhiambo PA, Orinda DA, Muruka FJ, Wasunna A. Retrospective study of carcinoma of the esophagus in Kenya. *Cancer Res* 1978 Feb;38(2):303-7.
- (59) Robertson MA, Harington JS, Bradshaw E. The cancer pattern in Africans at Baragwanath Hospital, Johannesburg. *Br J Cancer* 1971 Sep;25(3):377-84.
- (60) Cook P, Collis CH. Cancer of the oesophagus and alcoholic drinks in east Africa. *Lancet* 1972 May 6;1(7758):1014.
- (61) Cook PJ, Burkitt DP. Cancer in Africa. *Br Med Bull* 1971 Jan;27(1):14-20.
- (62) DAVIES JN, ELMES S, Hutt MS, MTIMAVALYE LA, OWOR R, SHAPER L. CANCER IN AN AFRICAN COMMUNITY, 1897--1956. AN ANALYSIS OF THE RECORDS OF MENGO HOSPITAL, KAMPALA, UGANDA. I. *Br Med J* 1964 Feb 1;1(5378):259-64.
- (63) Oettle AG. CANCER IN AFRICA, ESPECIALLY IN REGIONS SOUTH OF THE SAHARA. *J Natl Cancer Inst* 1964 Sep;33:383-439.
- (64) Sewram V, Sitas F, O'Connell D, Myers J. Tobacco and alcohol as risk factors for oesophageal cancer in a high incidence area in South Africa. *Cancer Epidemiol* 2016 Apr;41:113-21.
- (65) Vizcaino AP, Parkin DM, Skinner ME. Risk factors associated with oesophageal cancer in Bulawayo, Zimbabwe. *Br J Cancer* 1995 Sep;72(3):769-73.
- (66) Pacella-Norman R, Urban MI, Sitas F, Carrara H, Sur R, Hale M, Ruff P, Patel M, Newton R, Bull D, Beral V. Risk factors for oesophageal, lung, oral and laryngeal cancers in black South Africans. *Br J Cancer* 2002 Jun 5;86(11):1751-6.
- (67) Ocama P, Kagimu MM, Odida M, Wabinga H, Opio CK, Colebunders B, van IS, Colebunders R. Factors associated with carcinoma of the oesophagus at Mulago Hospital, Uganda. *Afr Health Sci* 2008 Jun;8(2):80-4.
- (68) Mlombe YB, Rosenberg NE, Wolf LL, Dzamalala CP, Chalulu K, Chisi J, Shaheen NJ, Hosseinipour MC, Shores CG. Environmental risk factors for oesophageal cancer in Malawi: A case-control study. *Malawi Med J* 2015 Sep;27(3):88-92.

- (69) 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;2013:503249.
- (70) Pampel F. Tobacco use in sub-Saharan Africa: estimates from the demographic health surveys. *Soc Sci Med* 2008 Apr;66(8):1772-83.
- (71) Sreeramareddy CT, Pradhan PM, Sin S. Prevalence, distribution, and social determinants of tobacco use in 30 sub-Saharan African countries. *BMC Med* 2014;12:243.
- (72) National Cancer Institute and Centers for Disease Control and Prevention. Smokeless Tobacco and Public Health: A Global Perspective. Chapter 12 Smokeless Tobacco Use in the African Region. Bethesda, MD: U.S.: Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, National Cancer Institute.; 2016. Report No.: NIH Publication No. 14-7983; 2014.
- (73) Idris AM, Ibrahim SO, Vasstrand EN, Johannessen AC, Lillehaug JR, Magnusson B, Wallstrom M, Hirsch JM, Nilsen R. The Swedish snus and the Sudanese toombak: are they different? *Oral Oncol* 1998 Nov;34(6):558-66.
- (74) Idris AM, Nair J, Ohshima H, Friesen M, Brouet I, Faustman EM, Bartsch H. Unusually high levels of carcinogenic tobacco-specific nitrosamines in Sudan snuff (toombak). *Carcinogenesis* 1991 Jun;12(6):1115-8.
- (75) Matsha T, Brink L, van RS, Hon D, Lombard C, Erasmus R. Traditional home-brewed beer consumption and iron status in patients with esophageal cancer and healthy control subjects from Transkei, South Africa. *Nutr Cancer* 2006;56(1):67-73.
- (76) USAID. An Inventory of Alcohol-Related Questions in the Demographic and Health Surveys and an Analysis of Alcohol Use and Unsafe Sex in Sub-Saharan Africa, DHS Analytical Studies 53. 2015 Sep 1.
- (77) Papas RK, Sidle JE, Wamalwa ES, Okumu TO, Bryant KL, Goulet JL, Maisto SA, Braithwaite RS, Justice AC. Estimating alcohol content of traditional brew in Western Kenya using culturally relevant methods: the case for cost over volume. *AIDS Behav* 2010 Aug;14(4):836-44.
- (78) Njue C, Voeten HA, Remes P. Disco funerals: a risk situation for HIV infection among youth in Kisumu, Kenya. *AIDS* 2009 Feb 20;23(4):505-9.
- (79) BURRELL RJ. Oesophageal cancer in the Bantu. *S Afr Med J* 1957 Apr 27;31(17):401-9.
- (80) Lo TQ, Oeltmann JE, Odhiambo FO, Beynon C, Pevzner E, Cain KP, Laserson KF, Phillips-Howard PA. Alcohol use, drunkenness and tobacco smoking in rural western Kenya. *Trop Med Int Health* 2013 Apr;18(4):506-15.
- (81) Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, Shakeri R, Pourshams A, Marjani HA, Nouraie M, Khatibian M, Semnani S, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer* 2008 Jun 3;98(11):1857-63.

- (82) van Rensburg SJ, Bradshaw ES, Bradshaw D, Rose EF. Oesophageal cancer in Zulu men, South Africa: a case-control study. *Br J Cancer* 1985 Mar;51(3):399-405.
- (83) Munishi MO, Hanisch R, Mapunda O, Ndyetabura T, Ndaro A, Schuz J, Kibiki G, McCormack V. Africa's oesophageal cancer corridor: Do hot beverages contribute? *Cancer Causes Control* 2015 Oct;26(10):1477-86.
- (84) Islami F, Pourshams A, Nasrollahzadeh D, Kamangar F, Fahimi S, Shakeri R, bedi-Ardekani B, Merat S, Vahedi H, Semnani S, Abnet CC, Brennan P, et al. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. *BMJ* 2009;338:b929.
- (85) Ali A, Ersumo T, Johnson O. Oesophageal carcinoma in Tikur Anbessa Hospital, Addis Ababa. *East Afr Med J* 1998 Oct;75(10):590-3.
- (86) Sewram V, Sitas F, O'Connell D, Myers J. Diet and esophageal cancer risk in the Eastern Cape Province of South Africa. *Nutr Cancer* 2014;66(5):791-9.
- (87) Joy EJM, Ander EL, Young SD, Black CR, Watts MJ, Chilimba ADC, Chilima B, Siyame EW, Kalimpira AA, Hurst R, Fairweather-Tait SJ, Stein AJ, et al. Dietary mineral supplies in Africa. *Physiol Plant* 2014;151:208-29.
- (88) Sammon AM. Protease inhibitors and carcinoma of the esophagus. *Cancer* 1998 Aug 1;83(3):405-8.
- (89) O'Neill C, Pan Q, Clarke G, Liu F, Hodges G, Ge M, Jordan P, Chang U, Newman R, Toulson E. Silica fragments from millet bran in mucosa surrounding oesophageal tumours in patients in northern China. *Lancet* 1982 May 29;1(8283):1202-6.
- (90) Hurst R, Siyame EW, Young SD, Chilimba AD, Joy EJ, Black CR, Ander EL, Watts MJ, Chilima B, Gondwe J, Kang'ombe D, Stein AJ, et al. Soil-type influences human selenium status and underlies widespread selenium deficiency risks in Malawi. *Sci Rep* 2013;3:1425.
- (91) Schaafsma T, Wakefield J, Hanisch R, Bray F, Schuz J, Joy EJ, Watts MJ, McCormack V. **Africa's Oesophageal Cancer Corridor: Geographic variations in incidence correlate with certain micronutrient deficiencies** . *PLoS One* 2015 Oct 1.
- (92) Mamiro P, Nyagaya M, Kimani P, Mamiro D, Jumbe T, Macha J, Chove B. Similarities in functional attributes and nutritional effects of magadi soda and bean debris-ash used in cooking African traditional dishes. *African Journal of Biotechnology* 2011 Feb 14;10(7):1181-5.
- (93) Sitas F, Egger S, Urban MI, Taylor PR, Abnet CC, Boffetta P, O'Connell DL, Whiteman DC, Brennan P, Malekzadeh R, Pawlita M, Dawsey SM, et al. InterSCOPE study: Associations between esophageal squamous cell carcinoma and human papillomavirus serological markers. *J Natl Cancer Inst* 2012 Jan 18;104(2):147-58.
- (94) Sitas F, Pacella-Norman R, Carrara H, Patel M, Ruff P, Sur R, Jentsch U, Hale M, Rowji P, Saffer D, Connor M, Bull D, et al. The spectrum of HIV-1 related cancers in South Africa. *Int J Cancer* 2000 Nov 1;88(3):489-92.

- (95) Mlombe Y, Dzamalala C, Chisi J, Othieno-Abinya N. Oesophageal cancer and Kaposi's sarcoma in Malawi: a comparative analysis. *Malawi Med J* 2009 Jun;21(2):66-8.
- (96) Ezzati M, Saleh H, Kammen DM. The contributions of emissions and spatial microenvironments to exposure to indoor air pollution from biomass combustion in Kenya. *Environ Health Perspect* 2000 Sep;108(9):833-9.
- (97) Dlamini Z, Bhoola K. Esophageal cancer in African blacks of Kwazulu Natal, South Africa: an epidemiological brief. *Ethn Dis* 2005;15(4):786-9.
- (98) Mureithi W, den Biggelaar C, Wesakania EW, Kamau K, Gatundu C. Management of trees used in mursik (fermented milk) production in Trans-Nzaoia district, Kenya. *J Ethnobiology* 2000;20(1):75-91.
- (99) Nieminen MT, Novak-Frazer L, Collins R, Dawsey SP, Dawsey SM, Abnet CC, White RE, Freedman ND, Mwachiro M, Bowyer P, Salaspuro M, Rautemaa R. Alcohol and acetaldehyde in African fermented milk mursik--a possible etiologic factor for high incidence of esophageal cancer in western Kenya. *Cancer Epidemiol Biomarkers Prev* 2013 Jan;22(1):69-75.
- (100) EFSA Panel on Contaminants in the Food Chain. Scientific Opinion on possible health risks for infants and young children from the presence of nitrates in leafy vegetables. *EFSA Journal* 2008 Jan 1;8(12):1935.
- (101) Matsha T, Stepien A, Blanco-Blanco E, Brink LT, Lombard CJ, van RS, Erasmus RT. Self-induced vomiting -- risk for oesophageal cancer? *S Afr Med J* 2006 Mar;96(3):209-12.
- (102) Yoder KM, Mabelya L, Robison VA, Dunipace AJ, Brizendine EJ, Stookey GK. Severe dental fluorosis in a Tanzanian population consuming water with negligible fluoride concentration. *Community Dent Oral Epidemiol* 1998 Dec;26(6):382-93.
- (103) Mwaniki DL, Courtney JM, Gaylor JD. Endemic fluorosis: an analysis of needs and possibilities based on case studies in Kenya. *Soc Sci Med* 1994 Sep;39(6):807-13.
- (104) PLOWRIGHT.W, Linsell CA, Peers FG. Focus of Rumenal Cancer in Kenyan Cattle. *British Journal of Cancer* 1971;25(1):72-&.
- (105) Bradshaw E, Schonland M. Smoking, drinking and oesophageal cancer in African males of Johannesburg, South Africa. *Br J Cancer* 1974 Aug;30(2):157-63.
- (106) Segal I, Reinach SG, de BM. Factors associated with oesophageal cancer in Soweto, South Africa. *Br J Cancer* 1988 Nov;58(5):681-6.
- (107) Sammon AM. A case-control study of diet and social factors in cancer of the esophagus in Transkei. *Cancer* 1992 Feb 15;69(4):860-5.

Table 1: Oesophageal squamous cell cancer (ESCC) incidence rates and numbers of new cases in 2012: African countries where the age-standardised incidence rate (ASR) is greater than the world's ASR in either gender and selected low-incidence African countries. Countries were not included if GLOBOCANs were not based on country-specific data.

Selected countries/ region#	Country (population in millions)	Men	Women	Men	Women	Men	Women	ASR Male: Female	Population subsets with higher incidence (number indicates location on map in Figure 1)
		Number of cases		ASR per 100,000		Rank of ESCC cases among all cancers			
ESCC estimates from histology-specific breakdown of oesophageal cancer in GLOBOCAN 2012 (21)									
World	World (7,054)	277944	119803	7.7	2.8	7	14	2.8	
ESCC-affected African countries†	Malawi (16)	1015	851	26.5	19.8	2	3	1.3	(h and i)
	Uganda (36)	1518	726	23.3	9.8	3	4	2.4	(b)
	Kenya (43)	1767	1481	19.3	14.3	3	3	1.3	Western Kenya (c), Bomet (d), Central (e), Nakuru (e)
	Botswana (2)	86	30	14.4	4.0	1	5	3.6	(l)
	South Africa (51)	2121	1425	12.9	6.2	4	6	2.1	Johannesburg (m), E.Cape, former Transkei (n)
	Tanzania (48)	1288	763	12.2	5.8	3	5	2.1	Kilimanjaro, Tanga, Arusha, Dar es Salaam (f and g)
	Mozambique (24)	685	493	11.8	6.7	3	5	1.8	-
	Zambia (14)	311	240	10.4	7.1	3	4	1.5	(j)
	Zimbabwe (13)	306	289	9.0	7.1	3	9	1.3	(k)
	Rwanda (11)	208	119	8.8	4.2	4	10	2.1	-
	Sudan (37)	373	434	4.0	4.1	6	5	1.0	-
	Ethiopia (87)	466	1077	1.9	4.4	11	8	0.4	Arsi (Asella 2430 m) and Bale zones (a)
Selected low ESCC incidence	Nigeria (167)	137	133	0.3	0.3	20	22	1.0	-
	Ghana (26)	68	17	0.8	0.2	14	24	4.0	-
	Guinea (11)	19	4	0.8	0.1	11	20	8.0	-
Cancer Incidence in 5 Continents estimates for oesophageal cancer (all histologies) – highest EC incidence countries (according to rates in men)									
	China, Cixian	2182	1387	192.7	108.5	1	1	1.8	-
	China, Yangcheng	1231	763	149.5	85.5	2	1	1.7	-
	China, Yanting	1591	1146	100.6	67.7	2	2	1.5	-
	Malawi, Blantyre	380	229	37.6	23.0	2	3	1.6	-
	South Africa, PROMEC	475	533	32.0	19.6	1	2	1.6	-
	Iran, Golestan	370	285	23.2	18.8	2	2	1.2	-
	Zimbabwe, Harare, African	182	103	22.2	15.3	4	7	1.5	-
	China, Zhongshan city	578	66	21.5	2.3	4	15	9.3	-
	India, Mizoram	347	58	20.9	3.7	3	6	5.6	-
	China, Jiashan	261	57	17.0	3.2	4	11	5.3	-
	Uganda, Kyadondo	157	125	15.6	11.5	5	7	1.4	-

Table 2: Case-control studies of oesophageal cancer (all histologies or squamous cell carcinoma only) conducted in sub-Saharan Africa.

	Country, location ^a	First author (associated reference)	Recruitment period	No. cases : controls	Tobacco	Alcohol	Household air pollution	HIV	Other findings
1	S. Africa – Gauteng	Oettlé (63)	1953-55	44 : 44	↑	↑	•	•	↑ in miners
2	S Africa – Gauteng	Bradshaw (105)	1963-?	196 : 1064	↑	↔	•	•	
3	Zimbabwe - Bulawayo ^b	Parkin; Vizcaino (32;65)	1963-77	881: 5238	↑	↔	•	•	↑ in miners
4	S. Africa – KwaZulu Natal	Van Rensburg (82)	1978-81	211 :211	↑	↑		•	↑ cigarettes, ↑ pipe, ↑ commercial maize
5	S. Africa – Gauteng	Segal (106)	1984-85	200 : 391	↑	↑	•	•	
6	S. Africa – E. Cape	Sammon; Sammon; (88;107)	1987-88	100 : 100	↑	↔	•	•	↑ solanum nigrum, ↑ trad. med
7	S. Africa - Gauteng	Pacella-Norman ; Sitas ; (66;94)	1995-99	405 : 2174	↑	↑	•	↔	
8	S. Africa - KwaZulu Natal	Dlamini (97)	~Early 2000?	87 : 121	↑	↑	↑	•	
9	S. Africa – E. Cape	Sewram; Sewram; (64;86)	2001-03	670 : 1188	↑	↑			↓ green leafy vegetables, ↓ fruit, ↑ maize+wild greens+ beans
10	S. Africa – E. Cape	Matsha (75)	Not stated	234 : 595	↑	↔	•		No assoc. with iron overload
11	Kenya, Eldoret	Patel (69)	2003-06	159 : 159	↑	↑	↑	↔	↑ hot drinks, ↑ tooth loss (unadj)
12	Uganda, Kampala	Ocama (67)	2004-05	55 : 232	↑	↔	•	•	
13	Malawi, Blantyre Lilongwe	Mlombe (68)	2011-13	96 : 180	↑		↑		↑ white maize flour
14	Zambia, Lusaka	Kayamba (30)	2013-14	50 : 50	↑	↑	↑	↑	

^a South African locations are named according to present-day provinces. E. Cape includes the former Transkei.

↑ increased risk. ↔ no association found. • not assessed;

^b based on men with non-missing information on tobacco (any type);

Table 3: Exposure sources to known or suspected oesophageal squamous cell carcinoma (ESCC)-risk factors across the African ESCC corridor

Type	Subtype	Exposure characteristics	Settings local terms and other observations										
Tobacco													
Smoking	Smoking of: commercial cigarettes, self-rolled cigarettes, pipes, cigars	Often bought in single/multiple sticks reverse smoking	<ul style="list-style-type: none"> All countries – commercial cigarettes, rolled cigarettes from loose tobacco Ethiopia – gaya: pipe smoking in Wollayita, shisha Kenya, Tanzania, Malawi –rolled cigarettes from home-grown tobacco Malawi - reverse smoking in women Prevalence (cigarette, pipe and others) of smoking (71) <p>Men / Women (%)</p> <table> <tr> <td>Ethiopia 6.8/0.6</td> <td>Kenya 18.7/0.4</td> </tr> <tr> <td>Malawi 17.7/0.4</td> <td>Rwanda 12.9/1.0</td> </tr> <tr> <td>Tanzania 19.6/0.5</td> <td>Uganda 14.2/1.2%</td> </tr> <tr> <td>Zambia 24.1/0.8</td> <td>Zimbabwe 22.0/0.2</td> </tr> <tr> <td>Mozambique 20.7/2.8</td> <td></td> </tr> </table>	Ethiopia 6.8/0.6	Kenya 18.7/0.4	Malawi 17.7/0.4	Rwanda 12.9/1.0	Tanzania 19.6/0.5	Uganda 14.2/1.2%	Zambia 24.1/0.8	Zimbabwe 22.0/0.2	Mozambique 20.7/2.8	
Ethiopia 6.8/0.6	Kenya 18.7/0.4												
Malawi 17.7/0.4	Rwanda 12.9/1.0												
Tanzania 19.6/0.5	Uganda 14.2/1.2%												
Zambia 24.1/0.8	Zimbabwe 22.0/0.2												
Mozambique 20.7/2.8													
Smokeless	Use of commercial and traditional snuff	Placed under tongue and in labio-dental groove	<ul style="list-style-type: none"> All countries –snuff (dry or moist) used orally and inhaled Ethiopia – snuff under tongue, common in the south Sudan – toombak (moist tobacco with sodium bicarbonate) Tanzania, Kenya - ugoro: moist oral snuff mixed with magadi salt used by older generations; gutka or thinso: tobacco with areca nut is chewed or placed in the cheek Uganda – dried or fresh tobacco leaves or ground tobacco with magadi salt placed in buccal cavity Uganda – taaba: dry nasal snuff smoked by Bakiga tribe S. Africa – nasal snuff by older women; dried tobacco and mokgako ash Prevalence of smokeless tobacco use (71) <p>Men/Women</p> <table> <tr> <td>Ethiopia 1.9/0.2</td> <td>Kenya 2.1/1.3</td> </tr> <tr> <td>Malawi 0.5/0.8</td> <td>Rwanda 5.8/2.7</td> </tr> <tr> <td>Tanzania 2.0/0.8</td> <td>Uganda 2.9/1.5</td> </tr> <tr> <td>Zambia 0.3/1.2</td> <td>Zimbabwe 1.6/0.4</td> </tr> <tr> <td>Mozambique 10.9/0.8</td> <td></td> </tr> </table>	Ethiopia 1.9/0.2	Kenya 2.1/1.3	Malawi 0.5/0.8	Rwanda 5.8/2.7	Tanzania 2.0/0.8	Uganda 2.9/1.5	Zambia 0.3/1.2	Zimbabwe 1.6/0.4	Mozambique 10.9/0.8	
Ethiopia 1.9/0.2	Kenya 2.1/1.3												
Malawi 0.5/0.8	Rwanda 5.8/2.7												
Tanzania 2.0/0.8	Uganda 2.9/1.5												
Zambia 0.3/1.2	Zimbabwe 1.6/0.4												
Mozambique 10.9/0.8													
		Chewed											
		Placed in nose											
Alcohol (in decreasing order of percentage alcohol-by-volume ABV)													
Commercial spirits (30-	Gin, whisky, brandy,	Consumed in plastic	Plastic sachets: local terms Zambia, Zimbabwe – tujilijili (or tujiri jiri), blackberries										

40% ABV)	consumed neat or mixed	packets (30 ml, 50 ml) or bottles (50 ml, 100 ml, 250 ml).	Tanzania, kiroba
High-ABV local home brews/distillations	distillation of sugar cane extract or molasses, palm or other fruits. Often consumed neat	Small shot (30 ml)	Kenya: changaa , kumi kumi Tanzania: gongo Ethiopia: arāqe or katikala (distilled from fermented cereals – ~ 40% ABV) Sudan: araqī - date gin Malawi, Zambia– kachasu or lutuku , a maize husks-based gin, jang’ala, chibuku Uganda – waragi (gin) South Africa - cidiviki
Wines (10-15%)	grape wine and banana wine	Banana wine (12% ABV) sold in 330ml recycled beer bottles; grape wine in 750 ml bottles, cereal wine	South Africa – grape wines Tanzania – banana wine; common as it is cheap and legal, used by older generations Kenya – muratina – honey based wine with muratina fruit Ethiopia – tej , fermented honey and gešo (buckthorn) (7-11% ABV)
Commercial beers (3-8% ABV)	wheat beer	– 330 ml ‘dumpies’, 750 ml magnums	
Low ABV home brews	consumed neat	Often in very large quantities, of 1L, 2L, or 5L jugs. Uganda, Itesots, drunk through straws from a large common pot	Tanzania, mbege (banana-based, variable ABV, generally low) Kenya and Tanzania, busaa (maize –based) Uganda, ujon (millet-based), often drunk from a large common pot through long straws , eg. by the Itesot tribe Sudan - mereesa Malawi – kadamsana Ethiopia – tela or tälla (2-4% ABV, barley and gešo fermentation)
Hot food and beverages			
Hot beverages	Tea and coffee	A high % fat in milk and high % milk and sugar in tea/coffee retains heat	Kenya, Tanzania, Malawi – milky tea, chai, which is stored on coals or in thermal flask poured directly into cup Ethiopia and Sudan – hot spicy coffee (eastern area)
Hot foods			Ethiopia – genfo : hot porridge Sudan – assida :hot porridge Malawi, South Africa – roasted maize cobs (eaten directly from the fire), mealie meal porridge
PAH			
Inhaled	Indoor air pollution		All countries - PAH levels influenced by fuel type (wood, charcoal from Acacia mearnsii and Newtonia buchananii trees, dung) and ventilation near fire (outdoors/indoors, windows, roof

wire mesh), hours spent cooking or sleeping by a fire.

Sudan – **dukhan** –acacia sauna

Ingested

Kenya - Mursik (Gachanja and Worsfold)

Tanzania - Charcoal to clean teeth (*makaa*)

Ethiopia – kolla (roasted cereals), kocho (flat bread cooed on a flat iron surface), home-roasted coffee

All - Barbecued foods, grilled to very well done/ burnt

Non-tobacco specific nitrosamines

Nitrate levels in leafy green vegetables (sukuma wiki, amanath, black nightshade) leading to endogenous production of nitrites and nitrosamines.

Smoked fish, especially near Lake Malawi, Lake Victoria.

Nitrates in drinking water, especially well water.

Figure 1: National-level map of age-standardized incidence rate (ASR) of oesophageal squamous cell carcinoma (ESCC) in women and men (Source: Arnold et al, GUT 2015). Superimposed are the locations of reported ESCC hotspots, which are indexed in Table 1.

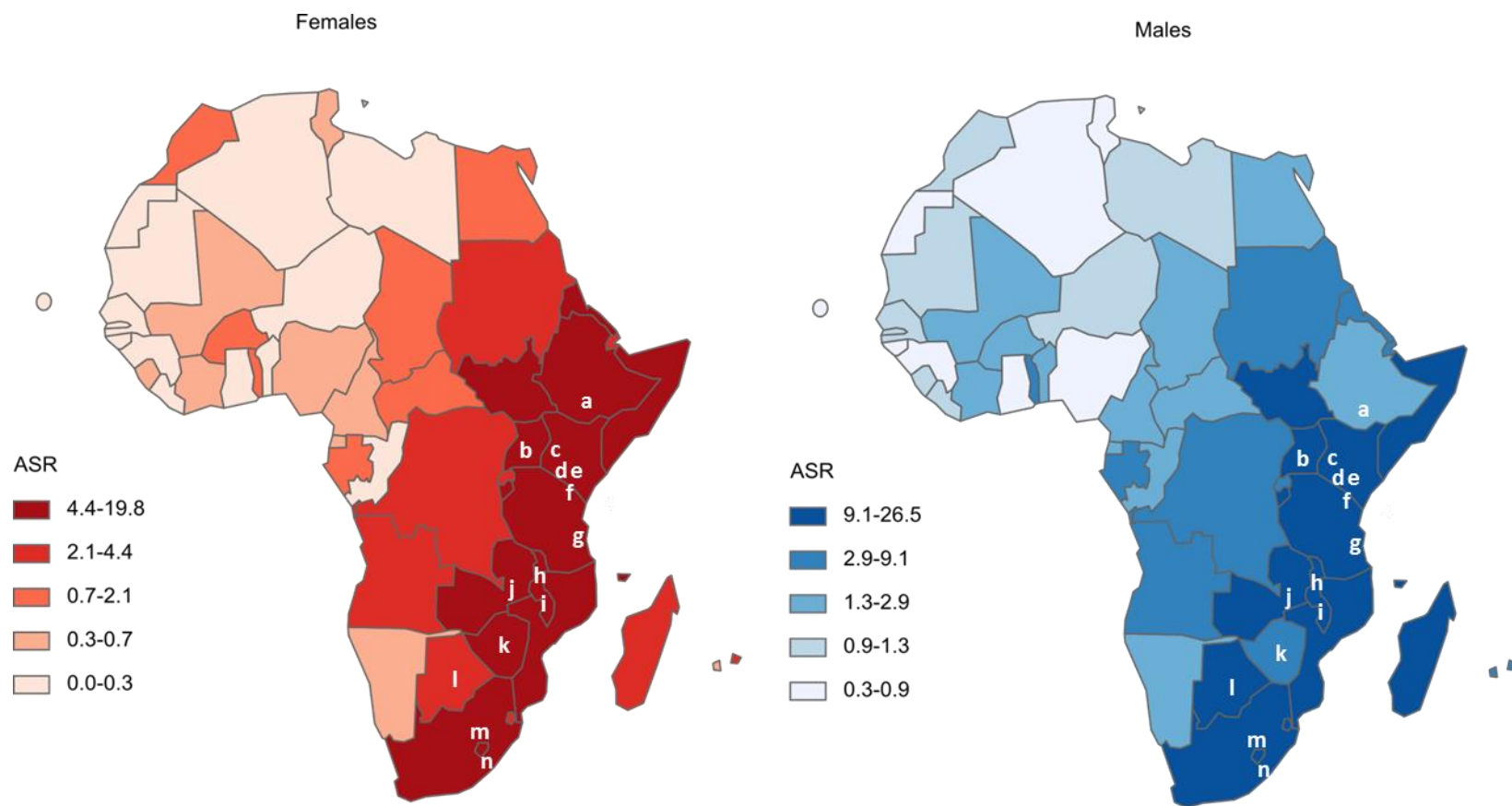


Figure 2: Oesophageal squamous cell carcinoma (ESCC) in Africa (source Arnold 2015): A. Age-standardized incidence rates (ASR) (world population) overall and by gender. B. Number of cases, by gender. C. Male:Female ratios of ASRs

