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

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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 ($\leq$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 Burrel 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 sheebeen 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* (fingermillet 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 that 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 B_3), 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/m^3 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 molybdenium-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 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 that 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.

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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	**-**

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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	• All countries – commerical 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 • Pravalence (cigarette, pipe and others) of smoking (71) ***Men / Women (%)*** 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 Chewed Placed in nose	• 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 • Pravalence of smokeless tobacco use (71) ***Men/Women*** 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
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 molases, palm or other fruits. Often consumed neat	Small shot (30 ml)	Kenya: **changaa, kumi kumi** Tanzania: **gongo** Ethiopia: **aräqe or katikala** (distilled from fermented cereals – ~ 40% ABV) Sudan: **araqi** - 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 mearnsil 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.

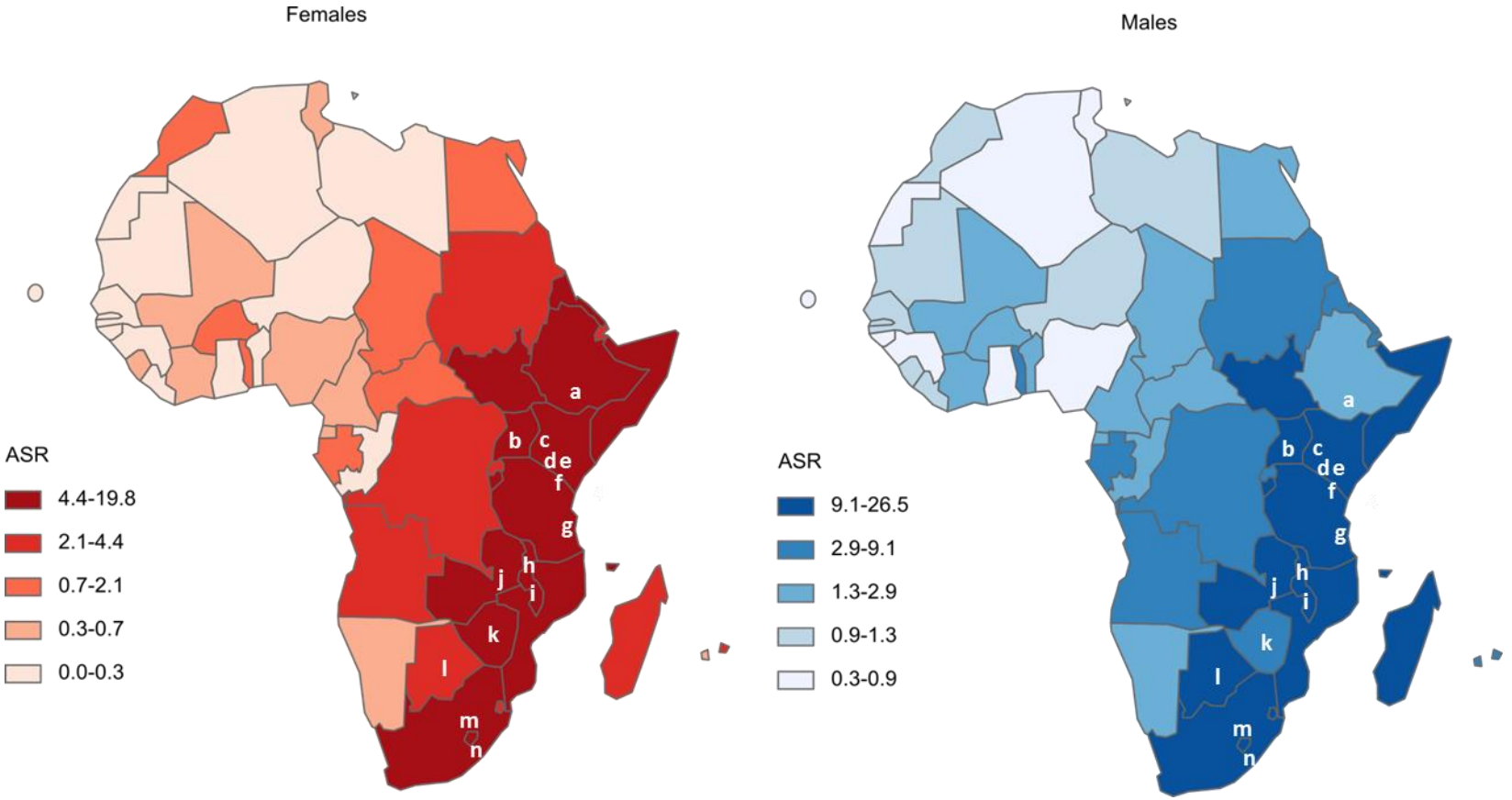

Figure 2: Oesophageal squamous cell carcinoma (ESCC) in Africa (source Arnold 2015): A. Age-standardized incidence rates (ASR) (world population) overall and by gender. B. Number of cases, by gender. C. Male:Female ratios of ASRs