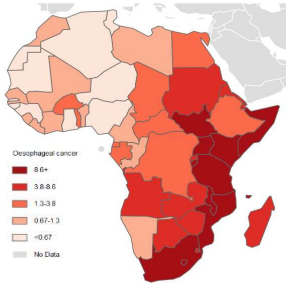
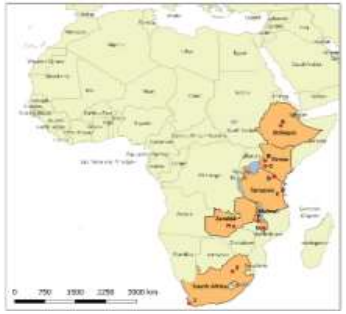
The African Esophageal Cancer Consortium (AfrECC)

Sandy Dawsey

African Cancer Research Webinar Series

April 16, 2020

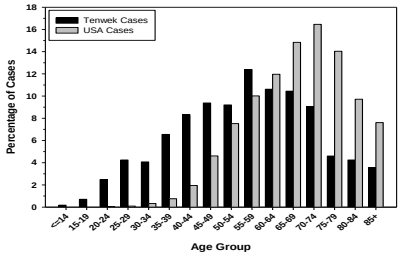




Introduction to the African Esophageal Cancer Consortium

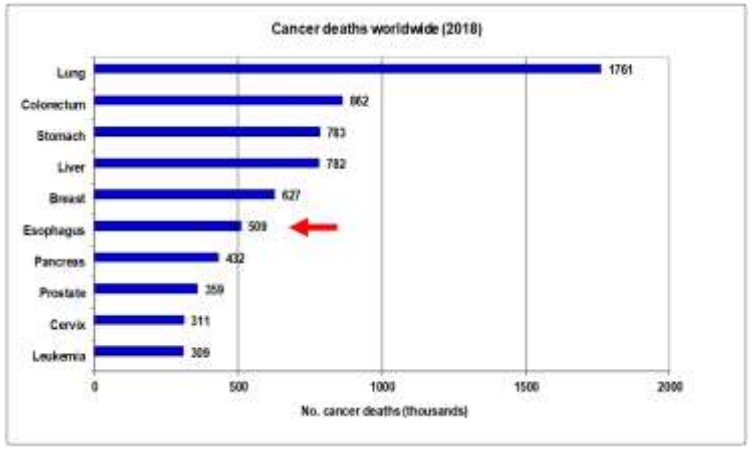
Presentation Outline

1. Background on Esophageal Cancer
2. Development of the African Esophageal Cancer Consortium (AfrECC)
3. Etiologic Studies
4. Esophageal Stenting for Palliation of Esophageal Cancer

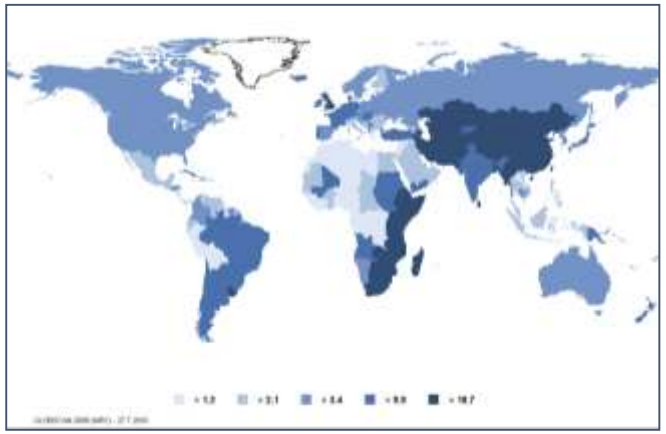


Esophageal Cancer

- 6th cause of cancer death
- 85% in developing countries
- 85% ESCC



- HR belts in Asia and Africa
  - Risk = 10-50x risk in LR pops
  - M:F = 1:1 - 2.5:1
  - 90% ESCC



ESCC Risk Factors

Low-Risk Populations

- Tobacco
- Alcohol
- Low SES

High-Risk Populations

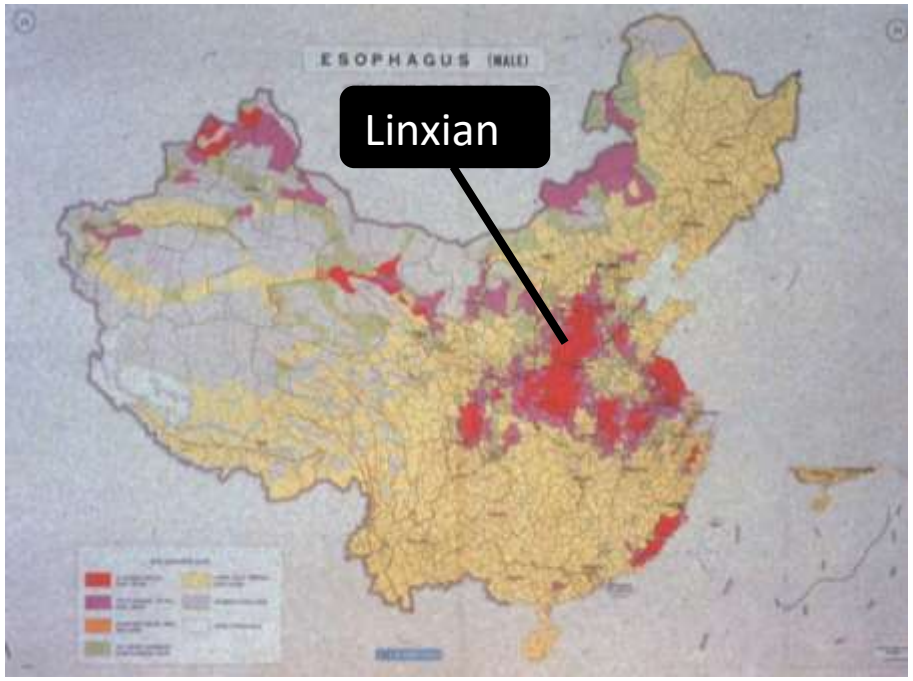
- [Tobacco, alcohol]
- Diet (low selenium)
- Tobacco carcinogens from non-tobacco sources (PAHs)
- Hot temperature drinks
- Poor oral health
- Low SES
- Family history
- Other?

Cigarette Smoking, Alcohol Drinking and ESCC in Low- and High-Risk Populations

Risk Factor	NIH-AARP [1] USA	NIT [2] China	GEMINI [3] Iran	Kashmir [4]
Current smoking	9.3 (4.0-21.3)	1.3 (1.2-1.5)	1.7 (1.1-2.7)	1.0 (0.6-1.6)
Current alcohol **>3 drinks/day**	4.9 (2.7-9.0)			
Ever consume alcohol?	76% of cohort	23% of cohort	2% of controls	0% controls

[1]Freedman AJE 2007; [2]Tran IJC 2005; [3]Nasrollahzadeh BJC 2008; [4]Dar BJC 2012

Selenium as a Risk Factor for ESCC in China

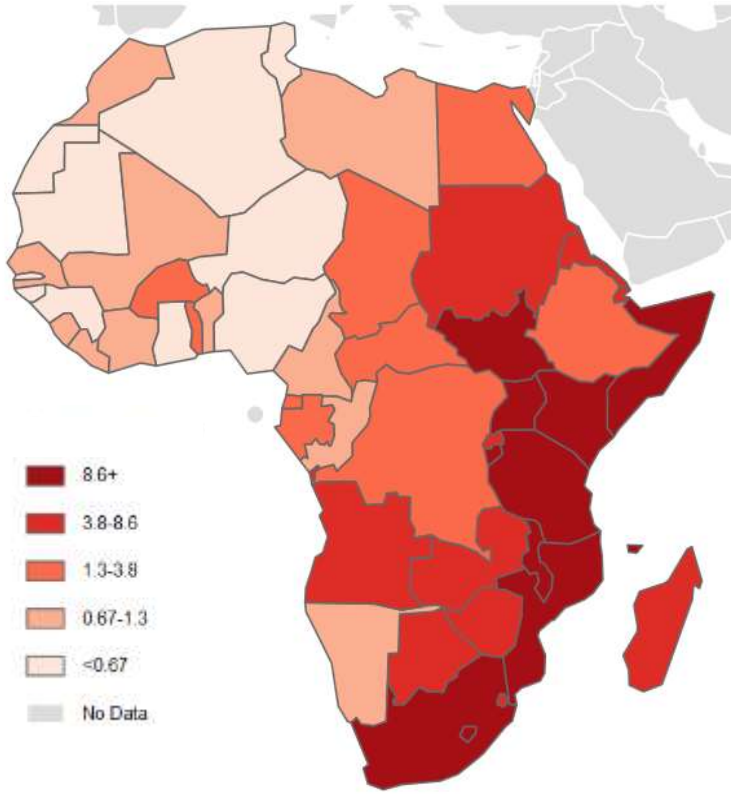


Esophageal cancer mortality

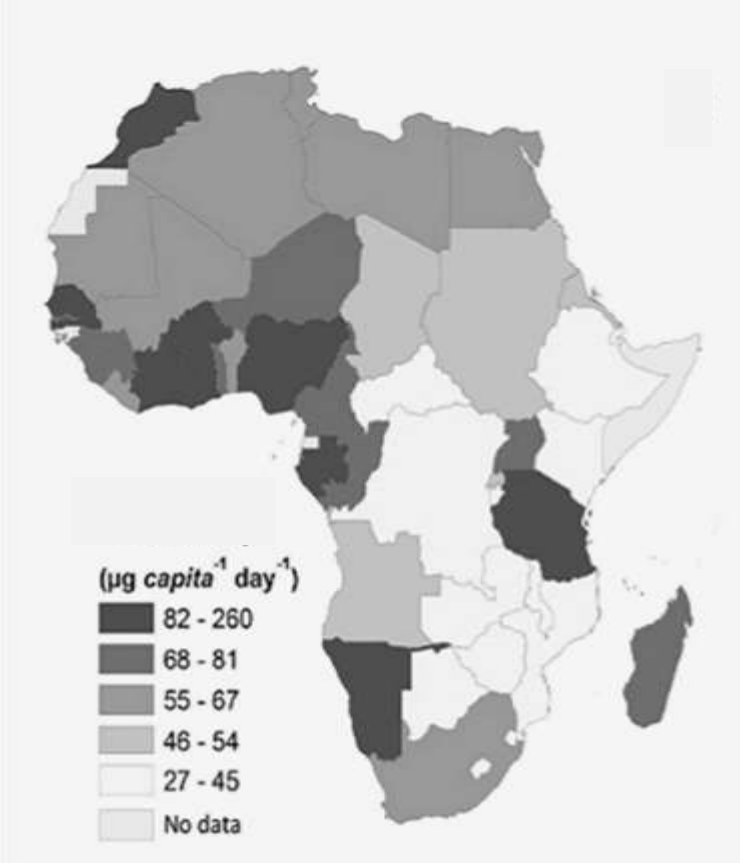
Soil selenium levels

- Serum Se (µg/L): Linxian = 72; sufficiency = 90; US = 124
- Randomized Trials show Se supplements reduce ESCC risk
- Population attributable risk for ESCC due to low Se = 26%

Selenium as a Risk Factor for ESCC in Africa



Esophageal cancer mortality



Dietary selenium

- Serum Se (µg/L): Kenya = 79; sufficiency = 90; US = 124

PAH Exposure and ESCC Risk

- Polycyclic aromatic hydrocarbons (PAHs) are carcinogenic byproducts of incomplete combustion of organic material, such as tobacco, gasoline, coal and wood
- Urine 1-hydroxypyrene glucuronide (1-OHPG) is a stable short-term biomarker of total body PAH exposure

Country	Population	Median 1-OHPG (pmol/ml)
Low-Risk		
Korea	Non-Smokers	0.26
US	Non-Smokers	0.23
Korea	Smokers	0.55
Korea	Smoking steelworkers	4.91
High-Risk		
China	Non-Smokers	3.36
Iran	General population	4.20
Brazil	General population	2.09
Kenya	General population	7.18

- High PAH exposure is a consistent finding in all HR pops

PAH Exposure and ESCC Risk

- PAH exposure appears to be a major universal risk factor for esophageal squamous cell carcinoma
- Different populations may acquire their main PAH exposure from different sources

Population	Primary exposure	Other exposures
West	Tobacco smoke	Car exhaust, Coal smoke
China	Coal smoke	Tobacco smoke, Car exhaust
Iran	???	Tobacco smoke, Car exhaust
Brazil	Tobacco smoke, Mate	BBQ meat, Car exhaust
Kenya	Wood smoke	Mursik

Tea Drinking Habits and ESCC Risk in the Golestan Case-Control Study

Exposure	Cases (%)	Control (%)	Adjusted OR (95% CI)
Tea temperature			
Warm (<65°C)	127 (43)	394 (69)	Reference
Hot (65-70°C)	108 (36)	155 (27)	2.07 (1.28-3.35)
Very hot (≥70°C)	63 (21)	19 (3)	8.16 (3.93-16.9)
Interval between pouring and drinking tea (min)			
≥ 4	132 (44)	394 (69)	Reference
2-3	112 (38)	138 (24)	2.49 (1.62-3.83)
< 2	54 (18)	35 (6)	5.41 (2.63-11.1)

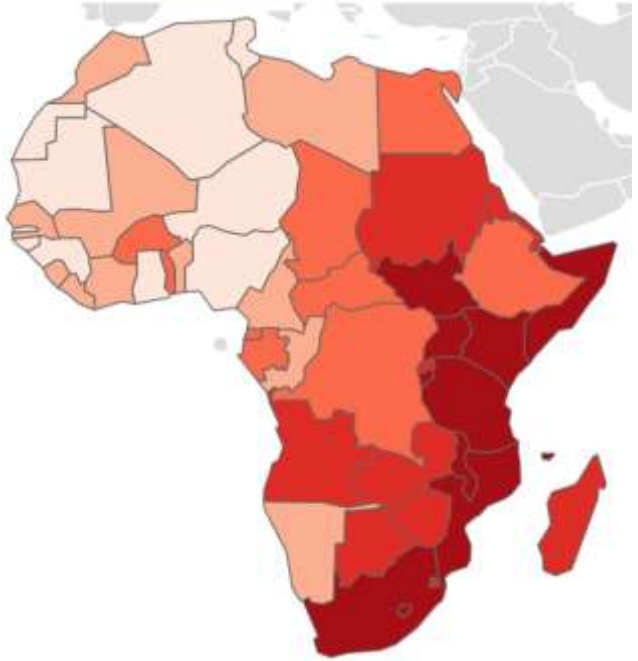
Mean temp = 62°C

Islami et al, BMJ 2009

ESCC Clinical Features

- Symptoms occur late
- Patients present late, usually obstructed
- Often the only treatment choice is palliation
- Usual survival after diagnosis is 3-6 mo
- Need early detection and treatment
- Need affordable and effective palliation

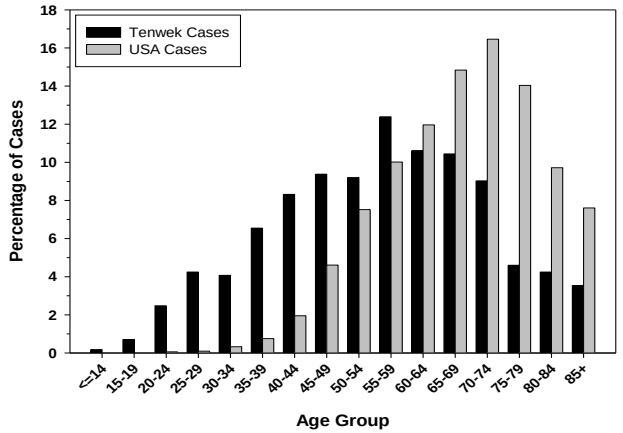
Esophageal Cancer in Africa



- A clear high-risk corridor ~ along the Rift Valley
- Tremendous genetic diversity
- Significantly understudied
- ~20% of cases <40 years old

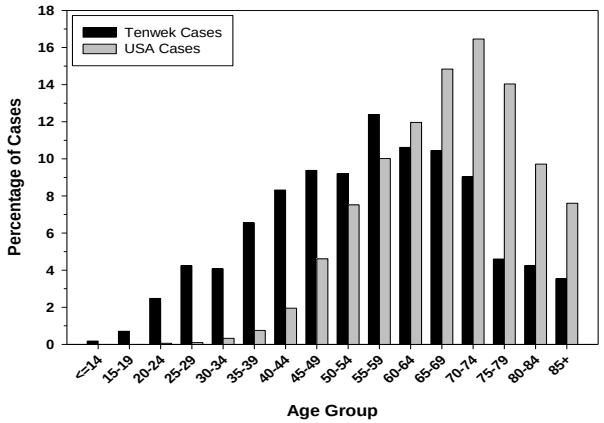
Age Distribution of ESCC cases at Tenwek Hospital in Western Kenya

- 400 ESCC cases/year, 90% unresectable
- A much younger age distribution than in Asia, Europe or the Americas



- At Tenwek, 17% of cases are <40, 7% are <30, and 1% are <20 years old
- Other hospitals in the African ESCC high-risk corridor report similar findings

Preliminary Studies at Tenwek Hospital



- Median serum Se = 79 µg/L
- Median urine 1-OHPG = 7.2 pmol/ml
- Mean tea temperature = 72^{o}C

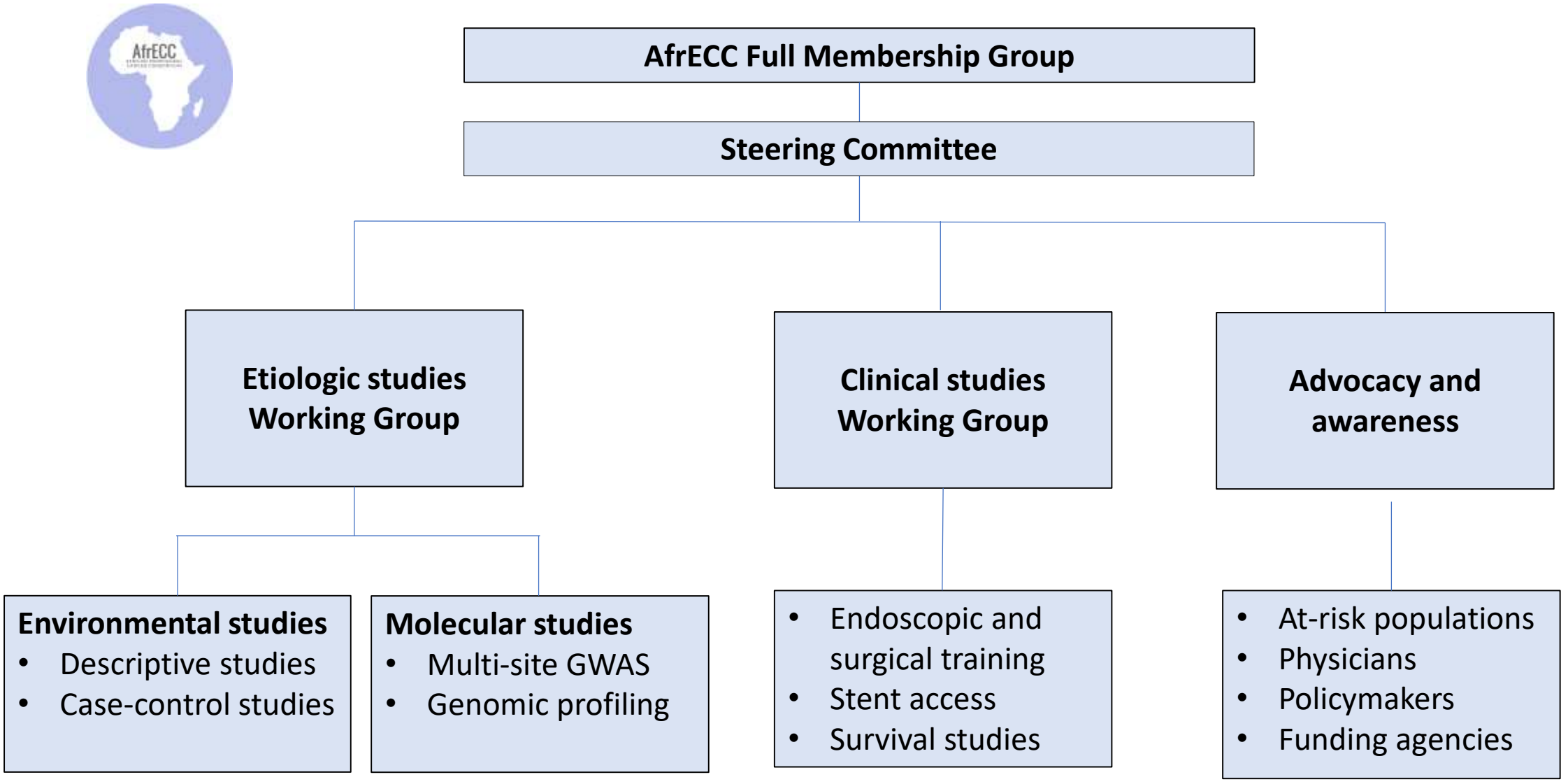
The African Esophageal Cancer Consortium (AfrECC)

Chronology:

2013 – AORTIC companion workshop of African and other investigators working on ESCC in Africa
2015 – AORTIC side meeting
2016 – NCI/IARC International Tumor Workshop → AfrECC formed

Goals

- Raise awareness of ESCC in Africa
- Support young African researchers
- Coordinate case-control studies
- Coordinate GWAS and genomic studies
- Coordinate training and capacity building
- Make affordable stents available throughout Africa
- Develop early detection and treatment programs


AfrECC Full Membership Group
Steering Committee
Etiologic studies Working Group
Clinical studies Working Group
Advocacy and awareness
Environmental studies
• Descriptive studies
• Case-control studies
Molecular studies
• Multi-site GWAS
• Genomic profiling
• Endoscopic and surgical training
• Stent access
• Survival studies
• At-risk populations
• Physicians
• Policymakers
• Funding agencies

Current AfrECC Activities

- 10 collaborating sites in 6 countries
- 5 international members (NCI, IARC, UCSF, UNC, Mayo)
- Bimonthly conference calls (20-30 people)
- Meetings every 2 years at AORTIC

- 7 case-control studies, 2 finished, 5 ongoing – total 2200 cases
- Harmonization of questionnaires in the 5 ongoing CCSs
- Mobile phone app for primary capture of all data

Current AfrECC Activities

- Joint GWAS study (collecting saliva, 2K/2K to be scanned in 2020)
- Biobanking for genomic studies

- Endoscopic capacity surveys
- Partnering with Boston Scientific and the ASGE to provide access to affordable stents and stent insertion training
- Quality of life and survival studies

The African Esophageal Cancer Consortium (AfrECC)

Etiologic Studies

1. Case-Control Studies
2. Multisite GWAS Study
3. Research Results
    a. Dental Fluorosis and Oral Health in the African EC Corridor
    b. High PAH Exposure in Kenya

Case-Control Studies

Site	Collaborator	Cases (total/now)	Controls (total/now)	Biosamples**
Eldoret, KE (B)	IARC	400/400	400/400	FFPE Bx, others?
Bomet, KE (C)*	NCI	200/180	200/180	FFPE Bx, Fr Bx, B, U, S
Moshi, TZ (D)*	IARC	300/300	300/300	FFPE Bx, B, U, S
Dar-es-Salaam TZ (E)	UCSF	400/400	400/400	FFPE Bx, Fr Bx, B, U, S
Lilongwe, MW (F)*	NCI, UNC	300/300	300/300	FFPE Bx, Fr Bx, B, U, S
Blantyre, MW (G)*	IARC	400/400	400/400	FFPE Bx, B, U, S
Lusaka, ZM (H)*		200/40	200/40	FFPE Bx, B, U, S

*Using standardized questionnaire and electronic data entry

**FFPE, formalin-fixed paraffin-embedded; Fr, frozen; Bx, biopsy; B, blood; U, urine; S, saliva

Multisite ESCC GWAS Study

- Target: 2000 cases/2000 controls
- Biosamples: Saliva (collected in Oragene kits) or Blood
- Analysis: H3 Africa chip, performed at NCI
- Replication: 1700 cases/6000 controls from Johannesburg (I), analyzed on the same chip by Chris Mathew in Johannesburg

Site	Collaborator	Cases (now)	Controls (now)	Sample Location
Eldoret, KE (B)	IARC	400	400	IARC
Bomet, KE (C)	NCI, Mayo	180	180	NCI, Mayo
Moshi, TZ (D)	IARC	300	300	IARC, Moshi
Dar-es-Salaam TZ (E)	UCSF	400	400	UCSF
Lilongwe, MW (F)	NCI, UNC	300	300	NCI
Blantyre, MW (G)	IARC	400	400	IARC, Blantyre
Total		1980	1980	

Dental Fluorosis and Oral Health in the African EC Corridor: Findings from the Kenya ESCCAPE Case-Control Study

Diana Menya, Stephen K Maina, … Joachim Schüz, and Valerie A McCormack
Moi University, AMPATH, and IARC

- 430 cases ≥ 18 yo with histo-confirmed ESCC presenting at MTRH in Eldoret, Kenya
- 440 age and sex frequency-matched controls (hospital inpatients, outpatients or visitors)
- Dental fluorosis
  - Irreversible hypomineralization of enamel due to exposure to water with excess fluoride (> 1.5 mg/L) during the development of permanent teeth (age 1-7 years)
  - High fluoride water comes from aquifers originating in high fluoride volcanic rocks (eg. the Rift Valley)
  - High altitude → more alkaline urine pH → ↓ renal excretion of fluoride
  - Clinical fluorosis is graded in 4 categories:
    - Normal (no fluorosis)
    - Mild fluorosis (brown opacities, without pitting)
    - Moderate fluorosis (small-medium pits)
    - Severe fluorosis (large pits with loss of enamel)

Meyna et al, Int J Cancer 2019

Dental Fluorosis and Oral Health in the African EC Corridor: Findings from the Kenya ESCCAPE Case-Control Study

Odds Ratios for ESCC associated with Oral Health Indicators and Water Source

Variable		Adjusted OR	95% CI
Tooth brushing	Weekly vs. Daily	2.3	(1.0, 5.5)
Tooth brush type	Stick vs. Commercial	1.7	(1.0, 2.9)
Decayed teeth	$\geq$ 3	8.8	(4.9, 15.8)
Missing teeth	$\geq$ 6	1.8	(1.0, 3.3)
DMFT	$\geq$ 8	5.7	(3.0, 10.9)
Mild fluorosis	all	2.3	(1.3, 4.0)
Mod/Sev fluorosis	all	9.4	(4.6, 19.1)
	DMFT < 4	2.5	(0.6, 10.1)
	DMFT $\geq$ 4	27.1	(9.6, 76.6
Water source	Spring/river (surface)	2.9	(1.5, 5.7)

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Meyna et al, Int J Cancer 2019

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Co-location of EC incidence and groundwater fluoride >1.5mg/L in Africa

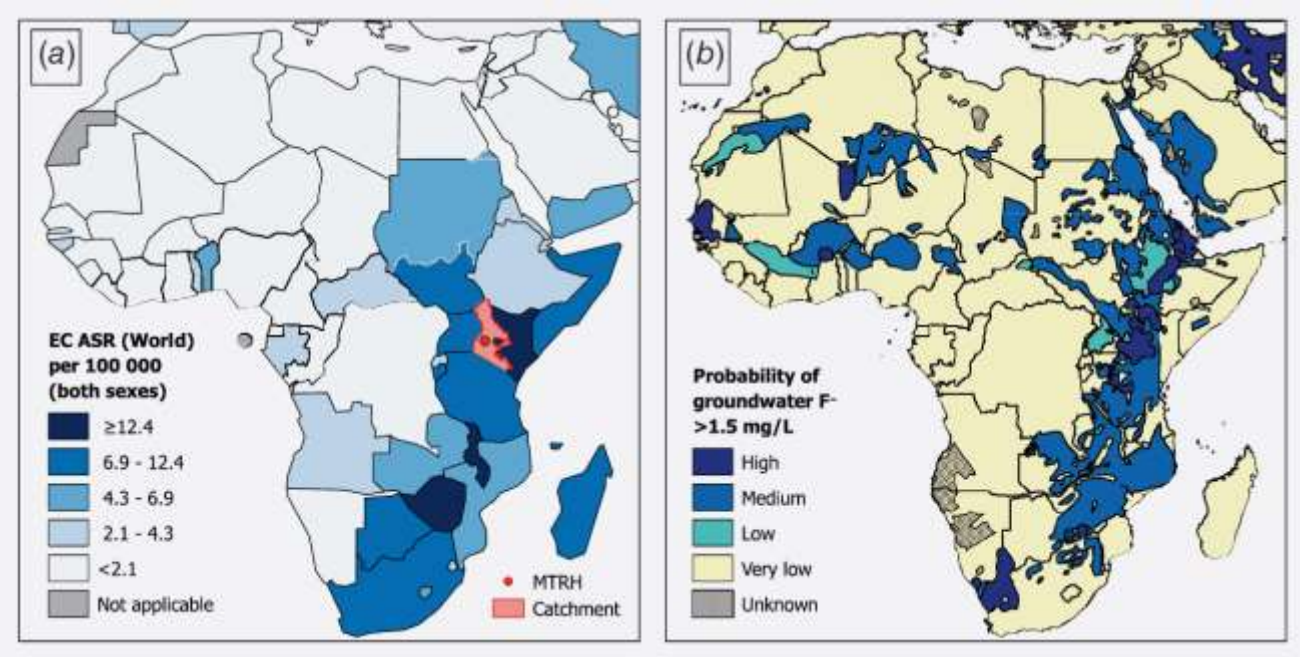
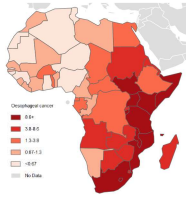


Figure 4. (a) Age-standardized incidence rates (ASR) of esophageal cancer (EC) in Africa, both sexes (Globocan 2018), indicating counties included in our the present study's catchment area; and (b) Risk of groundwater fluoride levels over 1.5 mg/L across Africa, reproduced with permission.

Meyna et al, Int J Cancer 2019

Dental Fluorosis and Oral Health in the African EC Corridor: Findings from the Kenya ESCCAPE Case-Control Study



Considerations

- This is the first report of dental fluorosis as a potential RF for ESCC
- There is no external evidence of fluoride carcinogenicity in humans
- Water with a high fluoride content may also contain other constituents that are carcinogenic
- The pits in moderate and severe fluorosis may house a life-long abnormal microbiome that produces carcinogenic by-products (acetaldehyde, nitrosamines, reactive oxygen species, etc.)

Opportunities for prevention

- Early education on the importance of oral hygiene
- Access to oral modern oral hygiene methods
- Access to piped water that has been treated to remove excess fluoride

Meyna et al, Int J Cancer 2019

High PAH exposure at Tenwek Hospital in Western Kenya

- Cross-sectional study of spot urines from 289 healthy adults
- Urine PAH metabolites were analyzed at the CDC lab that analyzes NHANES urines
- The metabolite levels in non-smokers were dramatically higher in western Kenya than those in ESCC high-risk populations in Brazil and Iran, and those in NHANES
- Age (<50), sex (female), indoor cooking (yes) and < primary education were associated with higher PAH metabolite levels
- Levels in Kenyan women were 2x those in Kenyan men and 10-30x those in US women
- The likely source is indoor air pollution (PAH exposure) from open cooking fires in unventilated kitchens
- *Potential interventions*: use enclosed cookstoves, chimneys, and more room ventilation

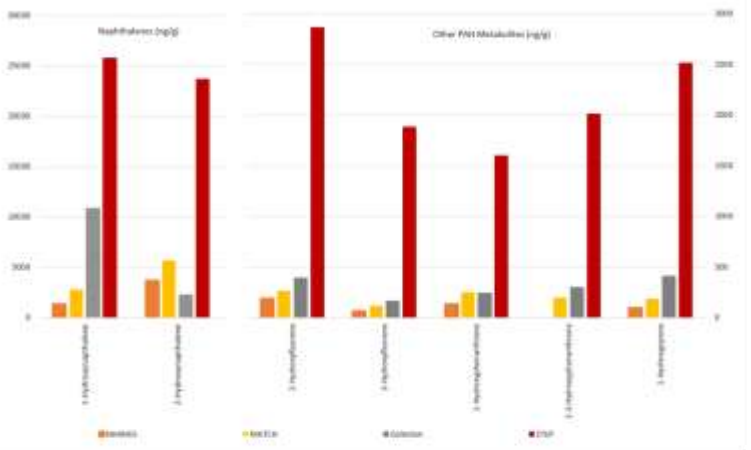


Figure 1. Geometric means of urinary PAH metabolites in nonsmokers from the NHANES study in the US, the MATCH study in Brazil, the Golestan CCS in Iran, and the STEP study in Kenya

Mwachiro, in preparation