

IARC Scientific Council SC/61

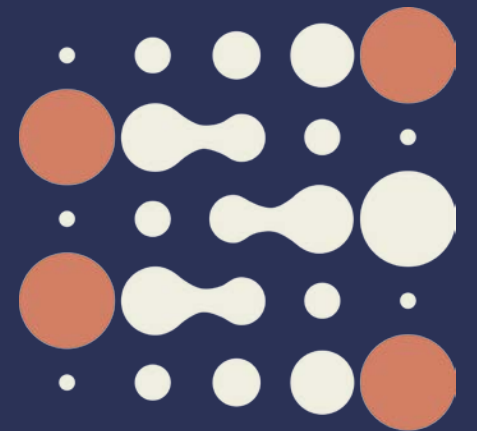
Item 14: Oesophageal Cancer, a long-neglected killer

Valerie McCormack

Joachim Schüz

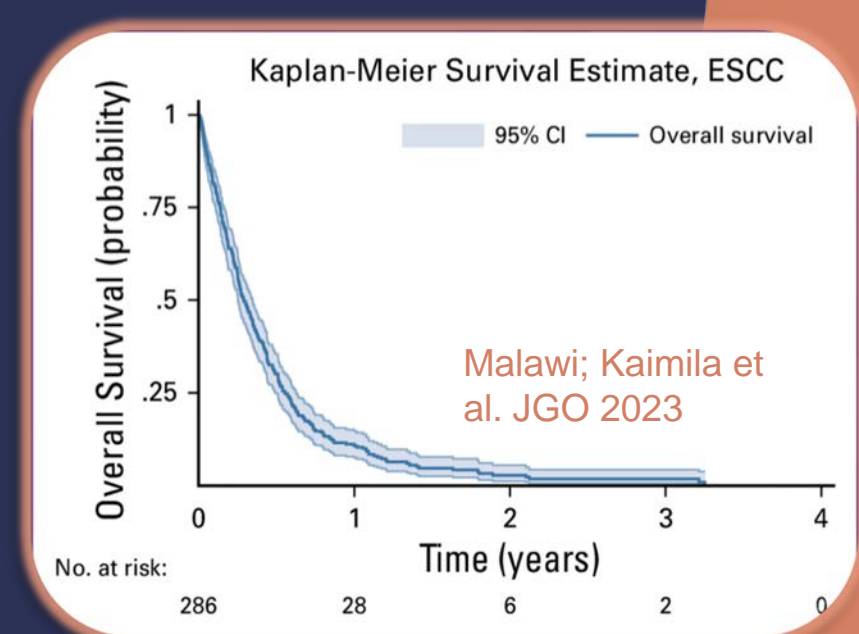
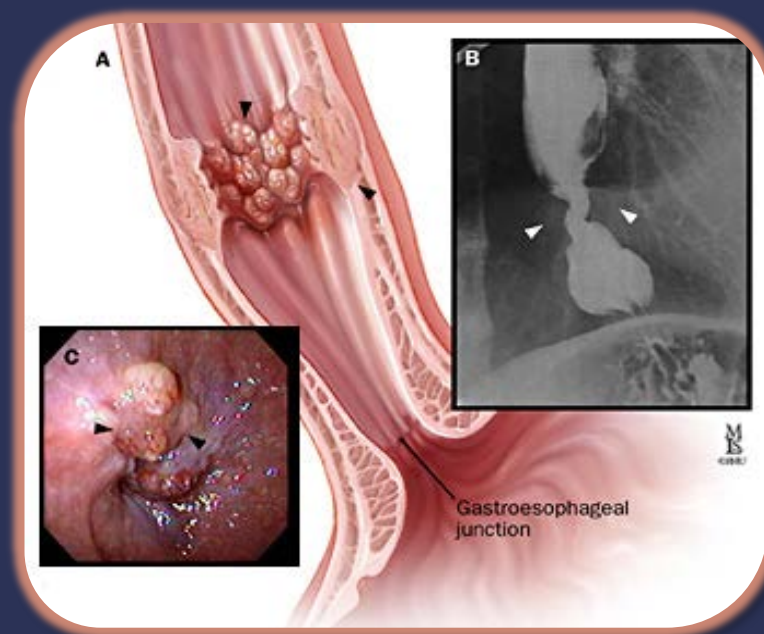
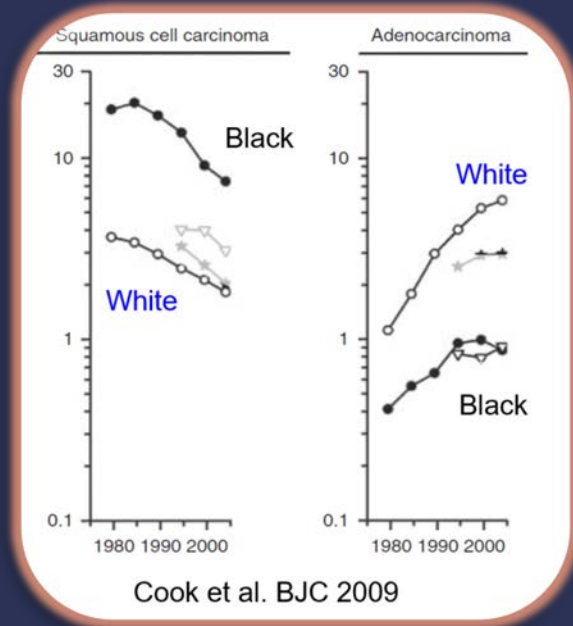
Behnoush Abedi-Ardekani

International Agency
for Research on Cancer



Essentials of Esophageal Cancer

- Two dominant histologies
 - >80% esophageal squamous cell carcinoma (ESCC)
 - <20% esophageal adenocarcinoma (EAC), but dominates in western countries and rising in men
- Poor prognosis; Treatment: surgery, radiotherapy +-chemotherapy; Stenting (palliative)
- Immense suffering: solid and liquid dysphagia



Global Burden of Oesophageal Cancer

- 511 000 new cases per year. Rank 11
- 450 000 deaths per year. Rank 7

High incidence defined by geography and poverty

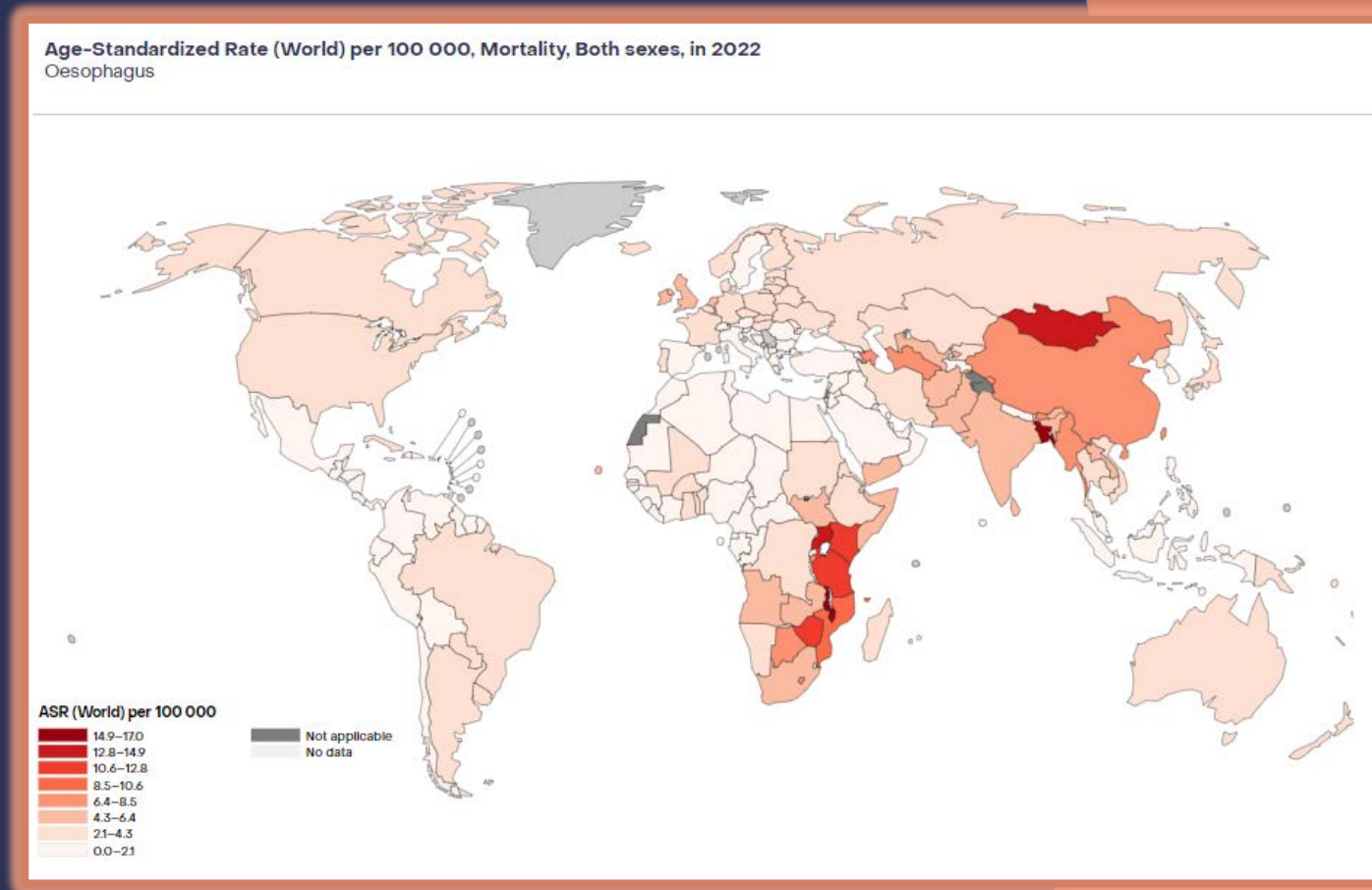
Young diagnosis in Africa

IARC activities:

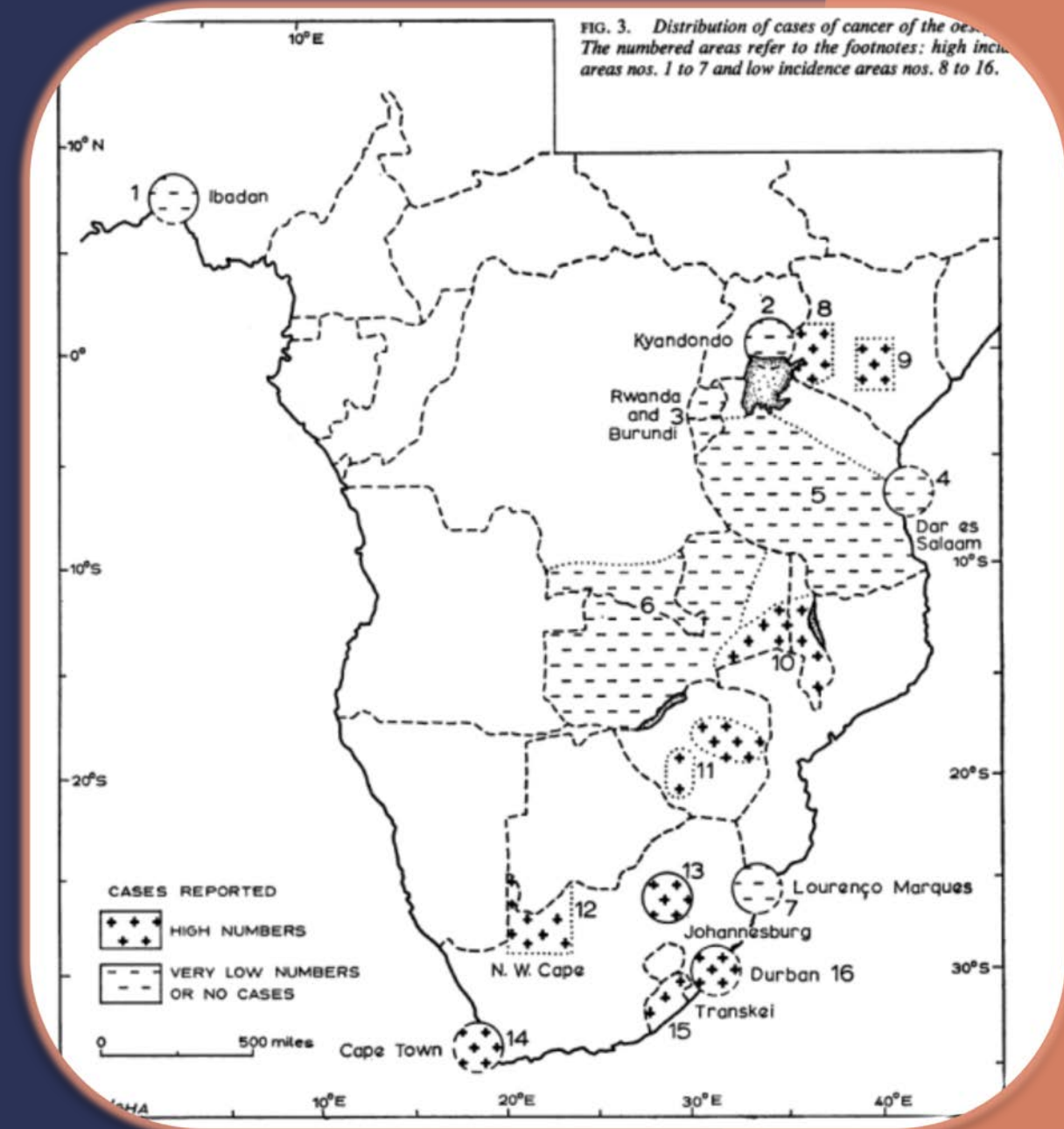
Golestan: Cohort and case-control studies

East Africa: ESCCAPE 1500 cases: 1500 controls

Mutographs - Brazil, China, Japan, UK, Africa



Neil McGlashan GUT 1969





Risk factors

- Alcohol
- Tobacco
- Opium (Iran)
- Family history
- Hot beverages (2A)
- Polycyclic aromatic hydrocarbons (ingested, indoor air pollution)
- Low fruit & vegetable

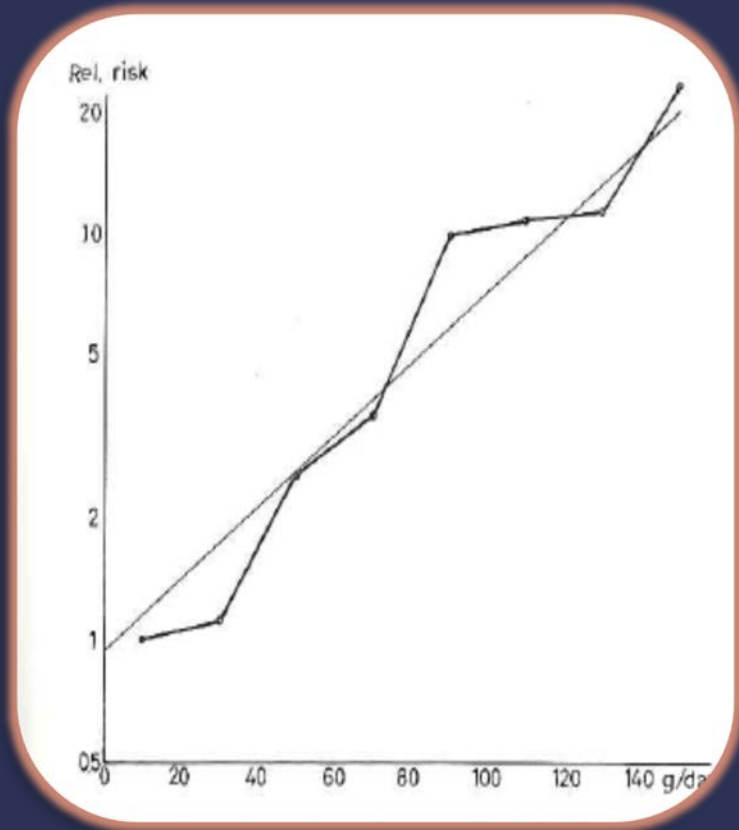
Risk markers – unclear mechanisms

- Low socio-economic position
- Rural residency
- Poor oral health incl dental fluorosis – microbiome?
- Animal contact
- Unpiped water supply
- Restricted diet -micronutrient deficiencies? mycotoxins? fumonisins?
- Pickled vegetables – N-nitroso compounds

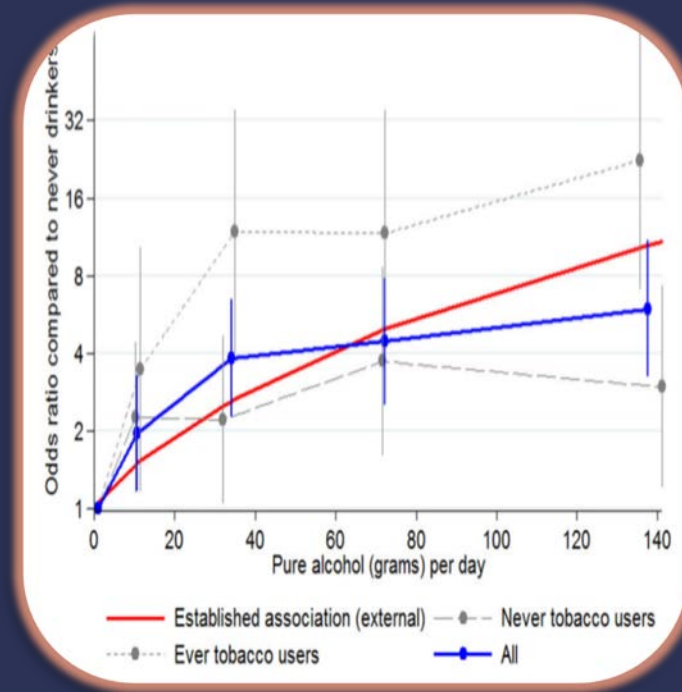


Many consistencies.....Alcohol

Int J Cancer 40 years apart!



Tuyns et al. Int J Cancer 1979.
Brittany and Normandy



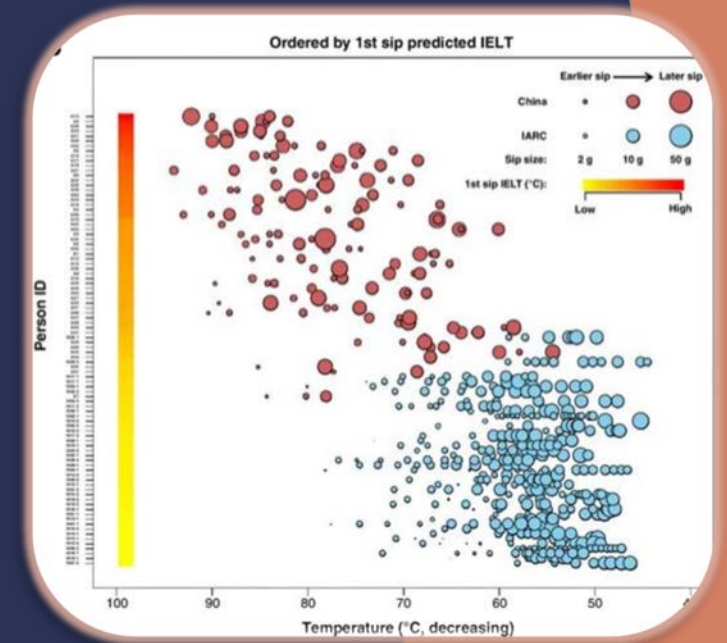
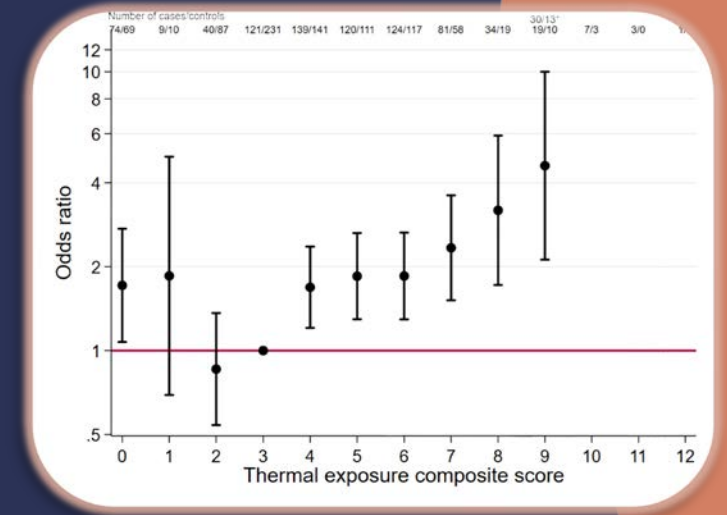
Menya et al. Int J Cancer 2019
Kenya



Kachasa distillation
Malawi

Hot beverages

- China and Africa: 70 to 80+ degrees Celsius at 1st sip
- First thermal exposure index (*Masukume et al, BJC 2022*):
Drinking speed, sip temperature, waiting time, burns
- First studies of hot beverage temperatures in children
- Public health messaging: Reducing both temperature **and** sip size is key to reduce intra-esophageal liquid temperature



Mutographs results

No evidence of a mutational signature indicative of an exogenous exposure to explain the differences in ESCC incidence

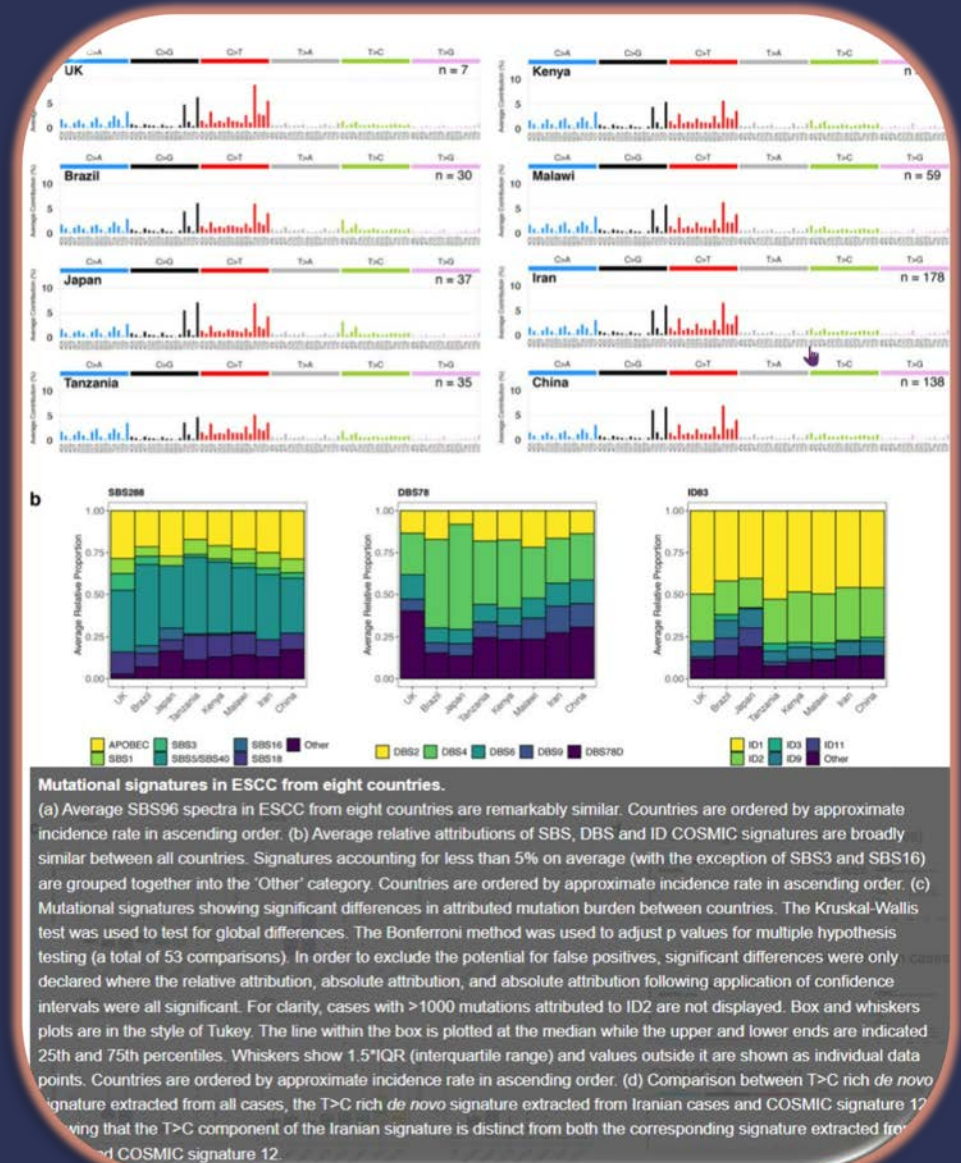
► Nat Genet. 2021 Nov;53(11):1553-1563. doi: 10.1038/s41588-021-00928-6. Epub 2021 Oct 18.

Mutational signatures in esophageal squamous cell carcinoma from eight countries with varying incidence

Sarah Moody ^{# 1}, Sergey Senkin ^{# 2}, S M Ashiquil Islam ^{3 4 5}, Jingwei Wang ¹, Dariush Nasrollahzadeh ^{2 6}, Ricardo Cortez Cardoso Penha ², Stephen Fitzgerald ¹, Erik N Bergstrom ^{3 4 5}, Joshua Atkins ², Yudou He ^{3 4 5}, Azhar Khandekar ^{3 4 5}, Karl Smith-Byrne ², Christine Carreira ⁷, Valerie Gaborieau ², Calli Latimer ¹, Emily Thomas ¹, Irina Abnizova ¹, Pauline E Bucciarelli ¹, David Jones ¹, Jon W Teague ¹, Behnoush Abedi-Ardekani ², Stefano Serra ⁸, Jean-Yves Scoazec ⁹, Hiva Saffar ¹⁰, Farid Azmoudeh-Ardalan ¹¹, Masoud Sotoudeh ⁶, Arash Nikmanesh ⁶, Hossein Poustchi ⁶, Ahmadrza Niavarani ⁶, Samad Gharavi ⁶, Michael Eden ¹², Paul Richman ¹³, Lia S Campos ¹⁴, Rebecca C Fitzgerald ¹⁵, Luis Felipe Ribeiro ¹⁶, Sheila Coelho Soares-Lima ¹⁶, Charles Dzamalala ¹⁷, Blandina Theophil Mmbaga ¹⁸, Tatsuhiko Shibata ¹⁹, Diana Menya ²⁰, Alisa M Goldstein ²¹, Nan Hu ²¹, Reza Malekzadeh ⁶, Abdolreza Fazel ²², Valerie McCormack ²³, James McKay ², Sandra Perdomo ², Ghislaine Scelo ^{2 24}, Estelle Chanudet ², Laura Humphreys ¹, Ludmil B Alexandrov ^{3 4 5}, Paul Brennan ², Michael R Stratton ²⁵

Affiliations + expand

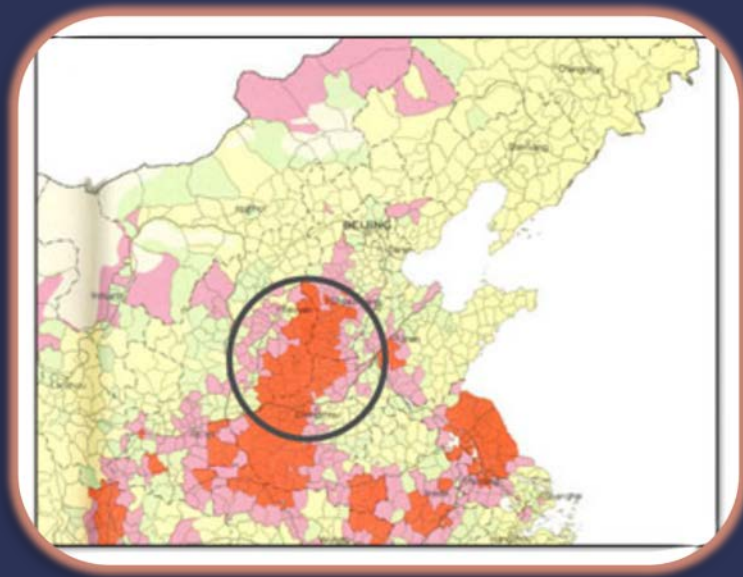
PMID: 34663923 DOI: 10.1038/s41588-021-00928-6



Many remaining mysteries.....

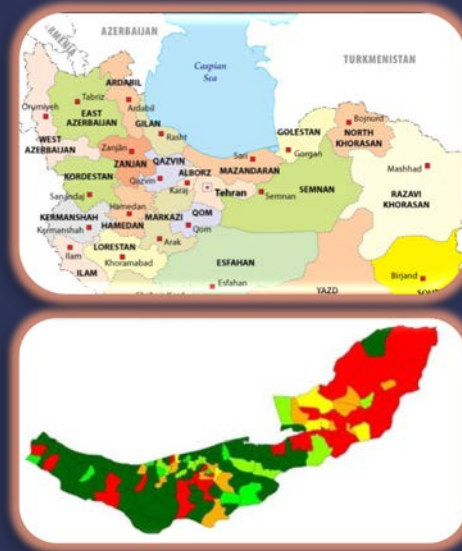
Localized ESCC hotspots with low male:female ratios

Chinese Cancer Atlas



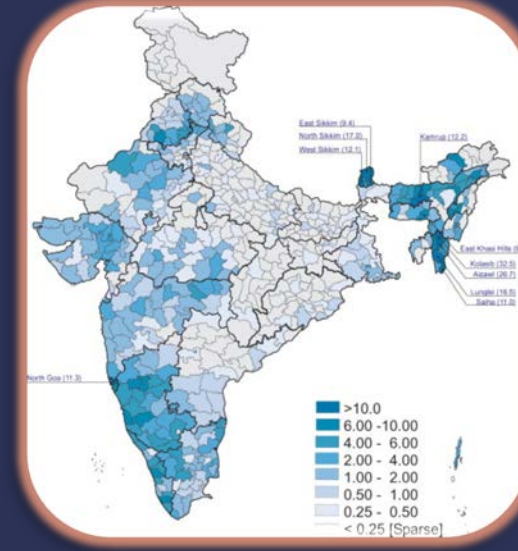
Linxian
Cixian

Central Asia

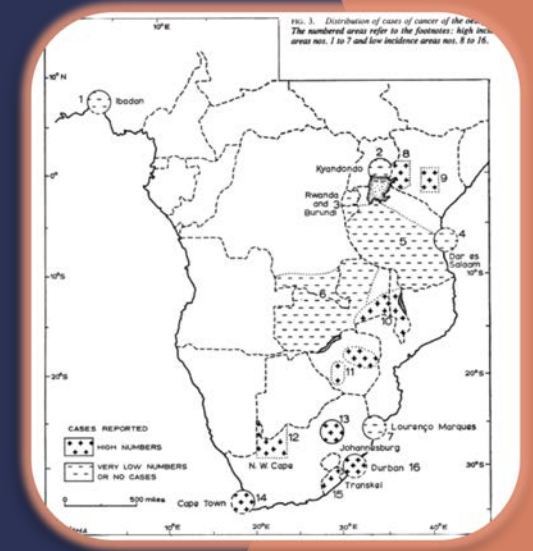


Iran, Golestan
Iran, Ardabil
Turkmenistan

India

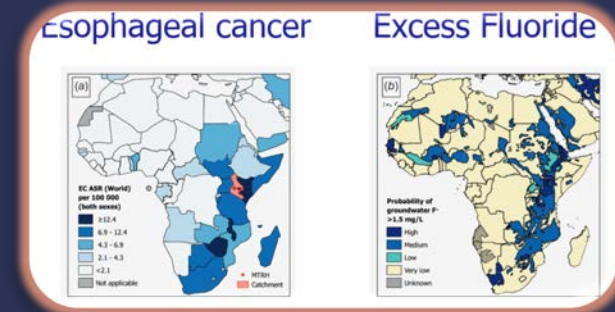


East & Southern Africa



Many remaining mysteries.....

- Micronutrient deficiencies
 - Primary selenium deficiency
 - Linxian Nutrition Intervention trials
 - How to identify their role in the absence of prospective cohorts?
- Unpiped water
- Dental fluorosis
 - Three independent positive associations in Africa (Menya IJC, Mmbaga IJC, Kaimila JGO)
 - What is dental fluorosis a marker of?
- Poor oral hygiene
- Why do the human hotspots have animal hotspots?



Spontaneous Squamous Carcinoma of the Esophagus in Chickens

C. A. RUBIO AND FU-SHENG LIU

A FOCUS OF RUMENAL CANCER IN KENYAN CATTLE

W. PLOWRIGHT, C. A. LINSELL AND F. G. PEERS

From the East African Veterinary Research Organization, Muguga, P.O. Kabele, Kenya; the Nairobi Regional Centre of the International Agency for Research on Cancer, P.O. Box 6831, Nairobi, Kenya; and the Tropical Products Institute, London

Ongoing...

Deciphering the promotional determinants of esophageal cancer in countries with varying incidence

Lead: GEM

Aim: To understand how hot liquids and other exposures promote the clonal selection of **pre-malignant cells in normal esophageal tissues**, leading to ESCC.

Rationale: Hot liquids are suspected to be a major risk factor for ESCC in high-incidence areas, but its underlying carcinogenic mechanisms remain unknown.

Description:

- Deep sequencing of 200 normal esophageal samples from seven high and low-risk countries.
- Analysis of clonal mutations in cases exposed to hot tea, mate, or soup among other risk factors.
- Spatial imaging approaches to characterize the tissue environment in exposed tissues.

Ongoing...

African Esophageal Cancer Consortium Pooling Project

Lead: ENV

Aim: To understand the aetiology of ESCC in Africa.

Description:

- Pooled data on 2500+ cases and 2500+ controls.
- Focus on groups of interest:
 - Risk factors < 40 years
 - Risk factors in non-drinkers non-tobacco users
- Novel risk factors: Geophagia, oral health, fluorosis,

Ongoing...

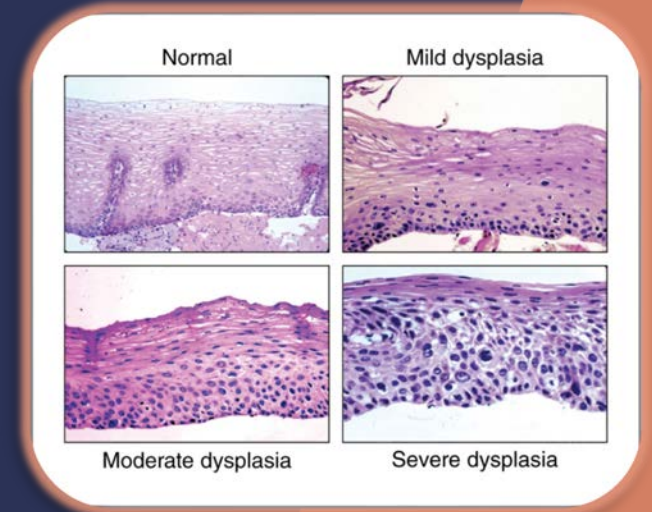
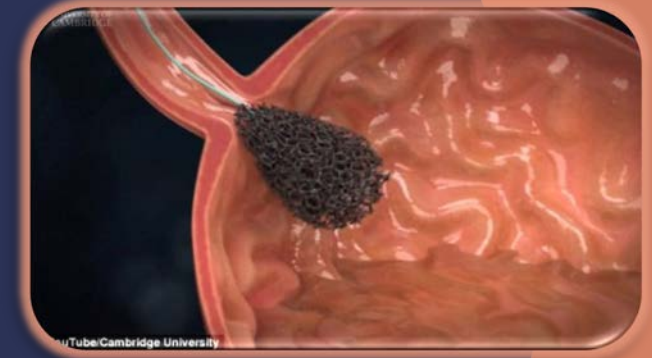
Sponge cytology for aetiology and early detection

Lead: ENV

Aim: To examine acceptability and feasibility of using sponge cytology as an appropriate health technology in the African setting

Description:

- 100 Volunteers in Tanzania swallowed the UK sponge. Excellent acceptability
- On-going comparison of UK vs Chinese sponge cytology



Proposals for IARC-led Esophageal Cancer Research 2025+

1. Impact of Covid-19 on ESCC and EAC
2. Enhanced EC case-control study in Malawi
3. Infections and ESCC in Africa
4. China-Africa-IARC ESCC collaboration for early detection

1. Impact of Covid-19 on Esophageal Cancer

Lead: CSU

Aim: To investigate the impact of COVID-19 on the diagnosis and survival of oesophageal cancer.

Description:

- Use existing population-based cancer registry data on incidence and survival
- Assess impact on stage at diagnosis and incidence
- Assess impact on survival
- Examine separately by histological subtype (EAC and ESCC)

Resources needed: 1-year postdoc €40,000



2. Enhanced Esophageal Cancer Case-Control study in Malawi

Lead: ENV, with NME, GEM, EGM

Aim: To expand ESCC aetiology from lifestyle factors (phase I, completed) to (i) home environmental exposures and (ii) incorporate a household proxy member for nutritional biomarkers and (iii) biobanking of tumour and non-tumour target tissue

Rationale: No cohorts in Africa. Need to obtain proxy biomarkers representative of habitual exposure (not possible in cases).

New case-control study

- Questionnaire + biospecimen + bring case and control home (logistically intense)
- Fieldwork over 2 years to achieve 600 cases and 600 controls

Location: Malawi Blantyre clinic has >300 incident ESCC patients per year. Highest incidence rates in globally. Male : Female 1.3:1

2. Continued

Environmental banking during home visit:

Drinking water, soil, staple, indoor air pollution using wrist band, sample of staple / grains

Biobanking investment:

Tumor biopsy + Non-tumor esophageal tissue + Blood

Case and control: blood sample and urine

Household member: blood and urine sample

Feasible with partners in place: Queen Elizabeth Central Hospital Endoscopy Unit, Kamuzu College of Health Sciences, African Esophageal Cancer Consortium, Queens University Belfast

Resources needed: Total (fieldwork investment phase): **€470 000**

3 years African postdoc at IARC : €120 000;

Training: €20 000 per year x2

Pollutant biomonitoring wristbands: €20 000

Fieldwork incl vehicle: €100 000 per year

Scopes: €40 000

Biospecimen storage + shipments: €30 000



3. Infections and ESCC in Africa

Lead: EGM, with ENV

Aim: To investigate the role of the infectome in ESCC development

Rationale: Infectious agents, including oncogenic viruses, are suspected to contribute to ESCC carcinogenesis

Description:

- Laboratory analysis (up to 250 infectious agents including viruses, bacteria, parasites). First hit on ***cytomegalovirus***.
- Plasma and biopsy samples from Ethiopia, Tanzania, Kenya); 200 analyzed, 400 to be completed.

Resources needed: Total : €100 000
1-year postdoc €40 000;
Laboratory: €60 000

Luminex
(250 biological agents)



4. China-Africa-IARC ESCC collaboration for early detection

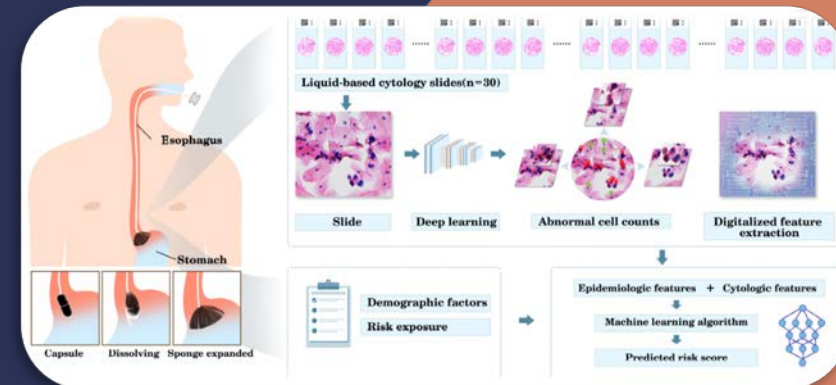
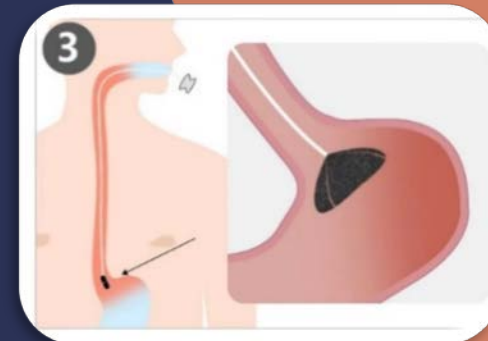
Aim: To share advances made in these two high-incidence settings

To plan studies to test whether the Chinese sponge AI early detection method (Gao et al 2023, Lancet Gastroenterology and Hepatology) has applications in the African setting

Proposal: Host an IARC-China-Africa ESCC early detection meeting in Malawi or Tanzania to assess:

- Equipment needs to use Chinese sponge, from swallowing to scan to uploading to a central AI platform
- Design of first pilot studies

Resources needed: €30 000



Thank you!

Thank you for your attention!

Thanks to the IARC Esophageal Cancer Team:
GEM, EGM, NME, CSU, ENV

Thank you to Gabriel Mukabana

Thank you for your support!

