

Reflux disease to esophageal cancer via genomics

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Esophageal cancer (EC): The seventh most common cancer and sixth leading cause of cancer death

World
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Research
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Continuous
Update
Project

Analysing research on cancer
prevention and survival

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Oesophageal cancer statistics

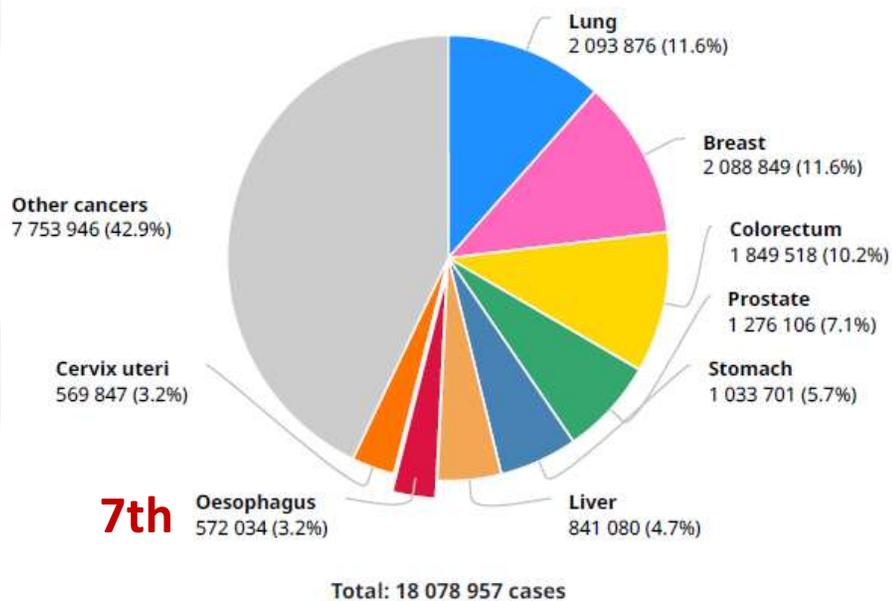
Oesophageal cancer is the seventh most common cancer worldwide

Oesophagus

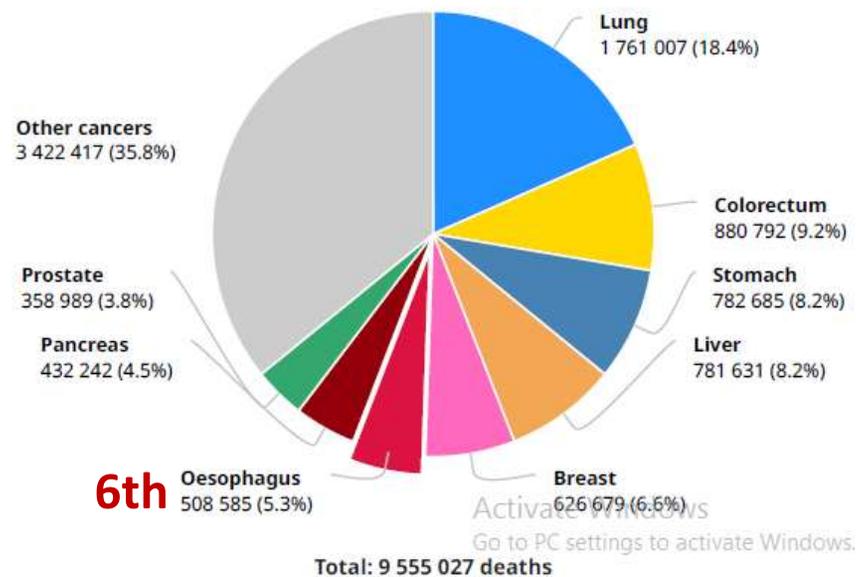
Source: Globocan 2018



Number of new cases in 2018, both sexes, all ages



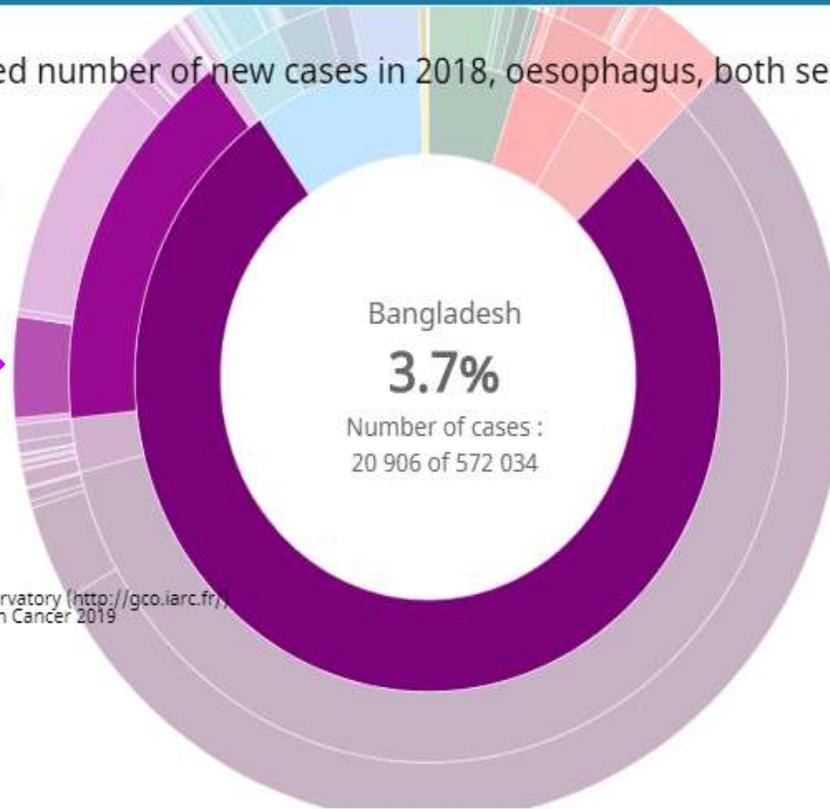
Number of deaths in 2018, both sexes, all ages





Estimated number of new cases in 2018, oesophagus, both sexes, all ages

- Global
- Africa
- Latin America and the Caribbean
- North America
- Asia
- Europe
- Oceania



Data source: GLOBOCAN 2018
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)
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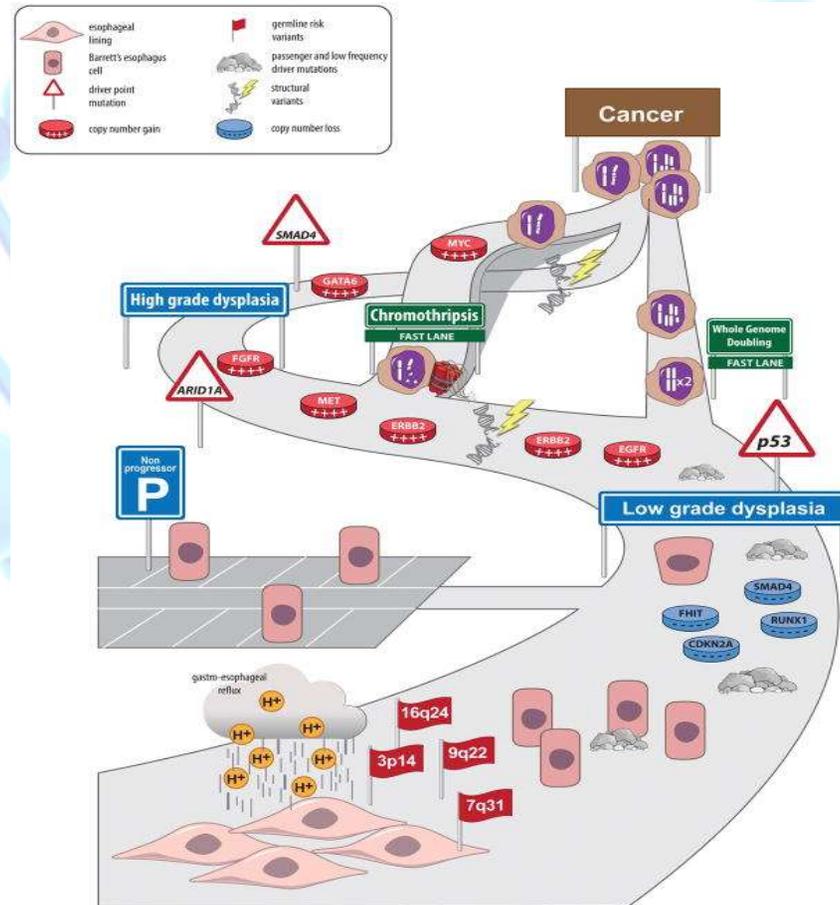
Esophageal adenocarcinomas (EAC)

In the western countries

- **The incidence has risen sharply in last four decades**
- **Increasing incidence of gastro-esophageal reflux disease and obesity**
- **More similar to the chromosomally unstable subtype of gastric carcinoma**

Studies of genomic characterization of EC

- Better understanding of pathogenesis of disease
- Identification of new therapeutic targets



Genomic studies of EAC

- **Large-scale, whole-genome, and whole-exome sequencing studies**
- **Conducted in the United States and United Kingdom**
- **Widespread chromosomal instability**
- **High mutational load in the EAC genome**
- **But only a limited number of recurrent tumor driver genes**

Important mutational signatures and genomic alterations

- **Important recurrent tumor driver genes include TP53, SMAD4, ARID1A, and CDKN2A**
- **A consistently high Adenine >Cytosine transversion rate at AA sites**
- **These changes are partly due to chronic inflammation and oxidative stress in response to acid reflux**

Other less frequent molecular subtypes

- **Molecular subtypes with potential therapeutic relevance**
 - **Enrichment for BRCA signature**
 - **Dominant Thymine>Guanine mutational pattern**
 - **Cytosine>Adenine/Thymine mutational pattern with evidence of an aging imprint**

Other less frequent molecular subtypes

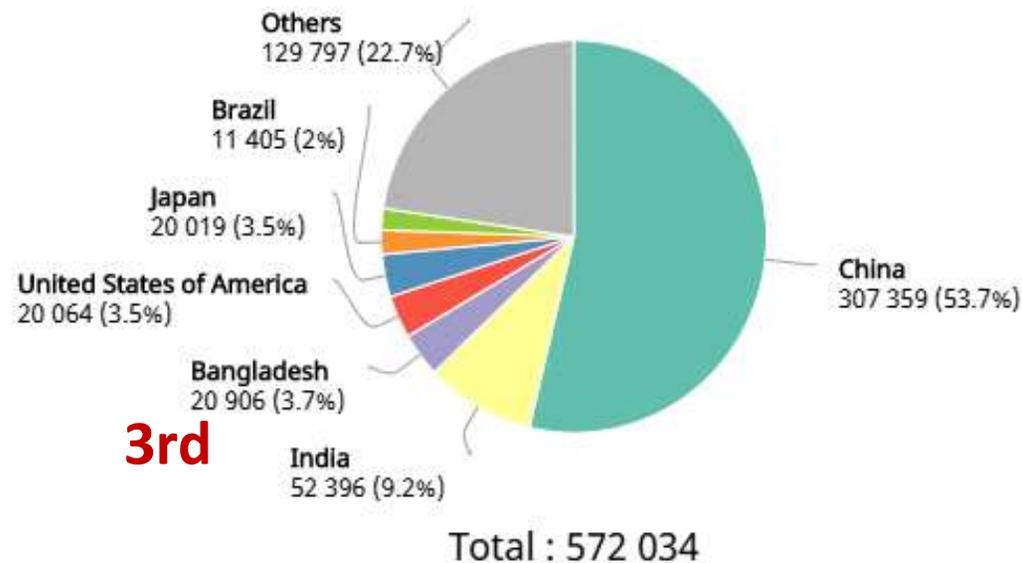
- **Chromothripsis:**
 - A genomic catastrophic event characterized by tens to hundreds of locally clustered DNA rearrangements
 - may have an important role in the malignant transformation of EAC

Esophageal cancer status in South East Asia

Several studies suggest that esophageal squamous cell carcinoma (ESCC) is the commonest subtype of esophageal cancer in South East Asia including Bangladesh

Bangladesh is in the third position

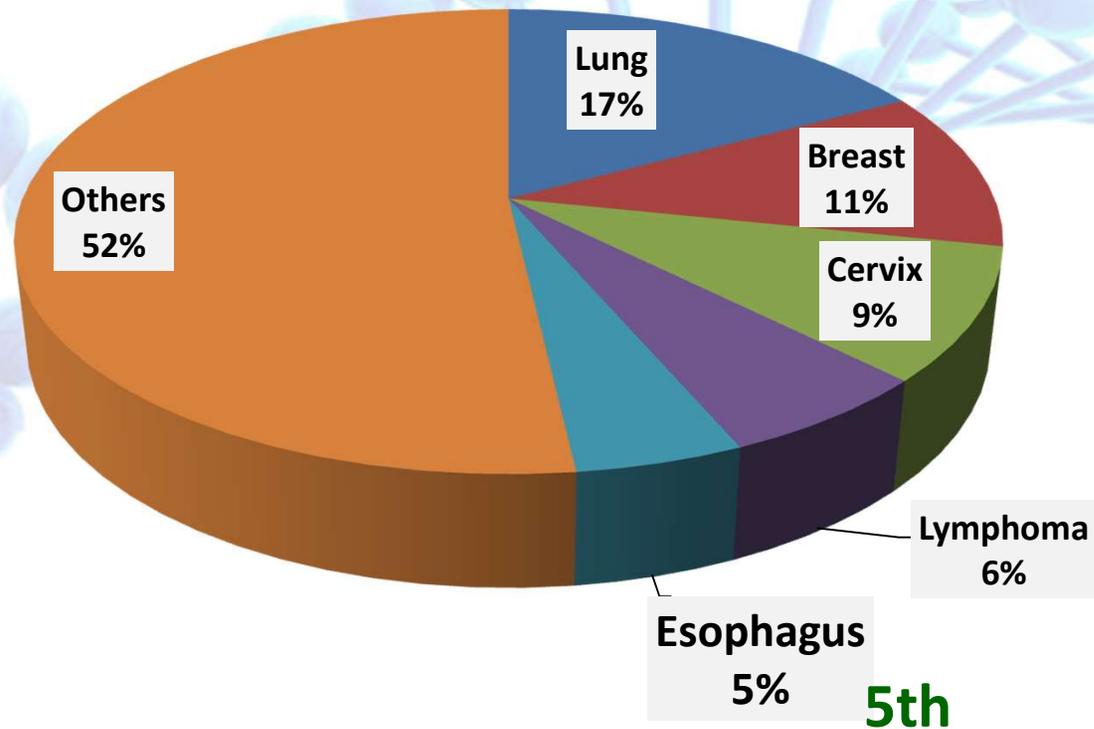
Estimated number of new cases in 2018, oesophagus, both sexes, all ages



Data source: GLOBOCAN 2018
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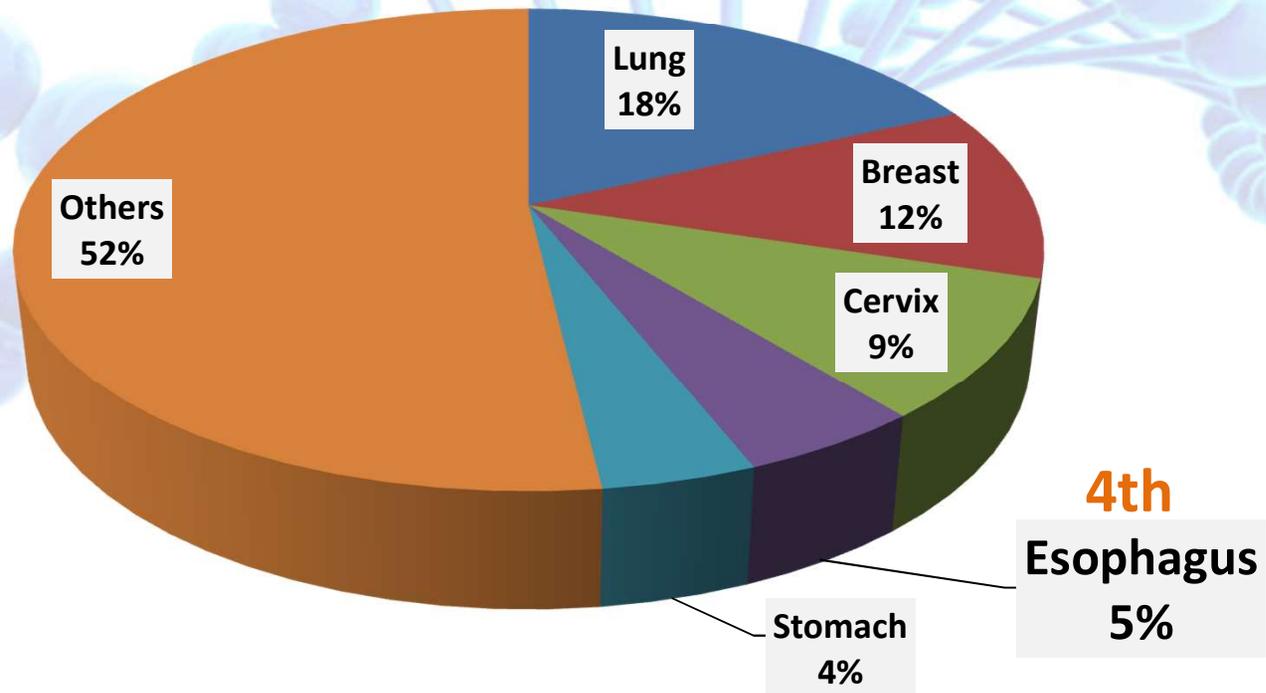
Hospital based cancer registry report

2005-2007

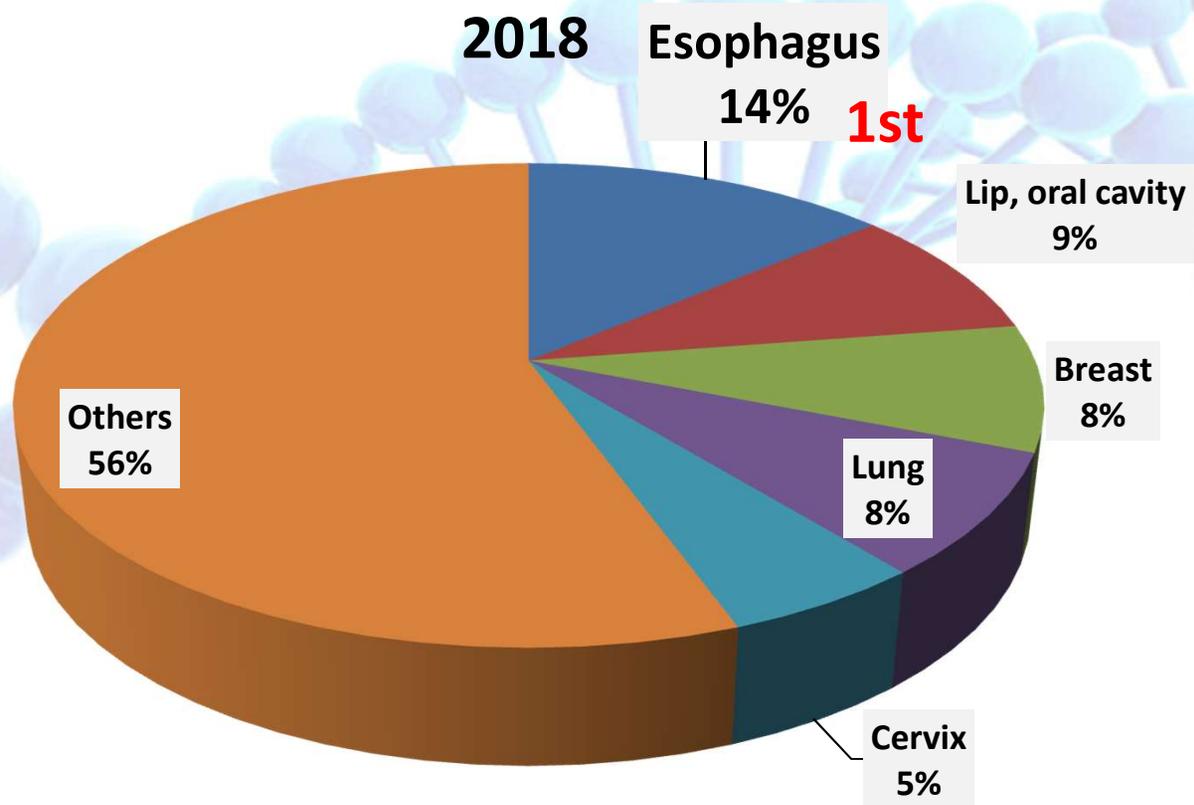


Hospital based cancer registry report

2008-2010



Globocan 2018



Bangladesh, Globocan 2018

- EC is the most prevalent cancer and the number one cause of cancer death
- Studies suggest that ESCC is the commonest subtype

Whole genome sequencing in Chinese EAC patients

- The genetic mutations in Asian EAC are different from that in western EAC
- Indicates different mechanism of malignant transformation in Asian EAC



ARTICLE

DOI: [10.1038/s42003-018-0182-8](https://doi.org/10.1038/s42003-018-0182-8)

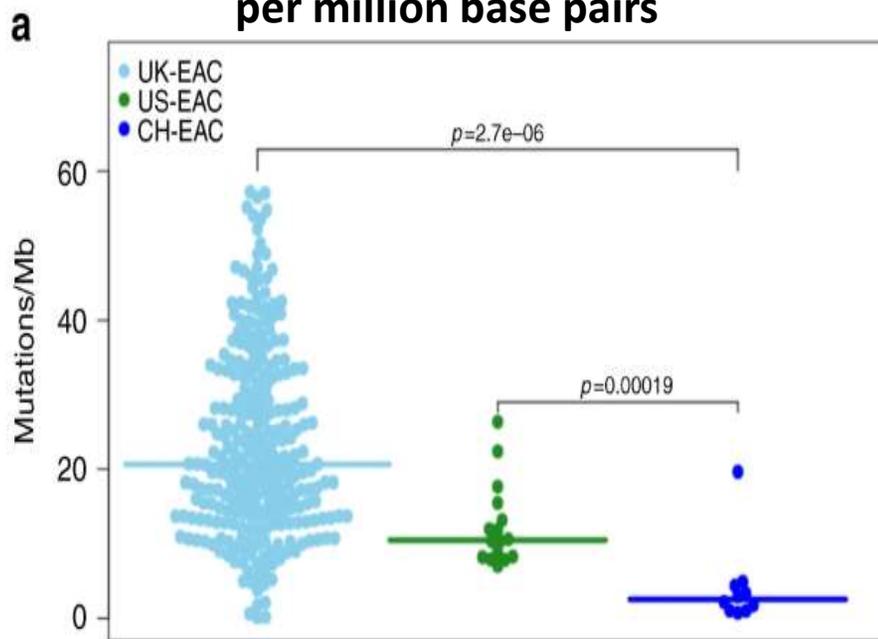
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Whole-genome sequencing of esophageal adenocarcinoma in Chinese patients reveals distinct mutational signatures and genomic alterations

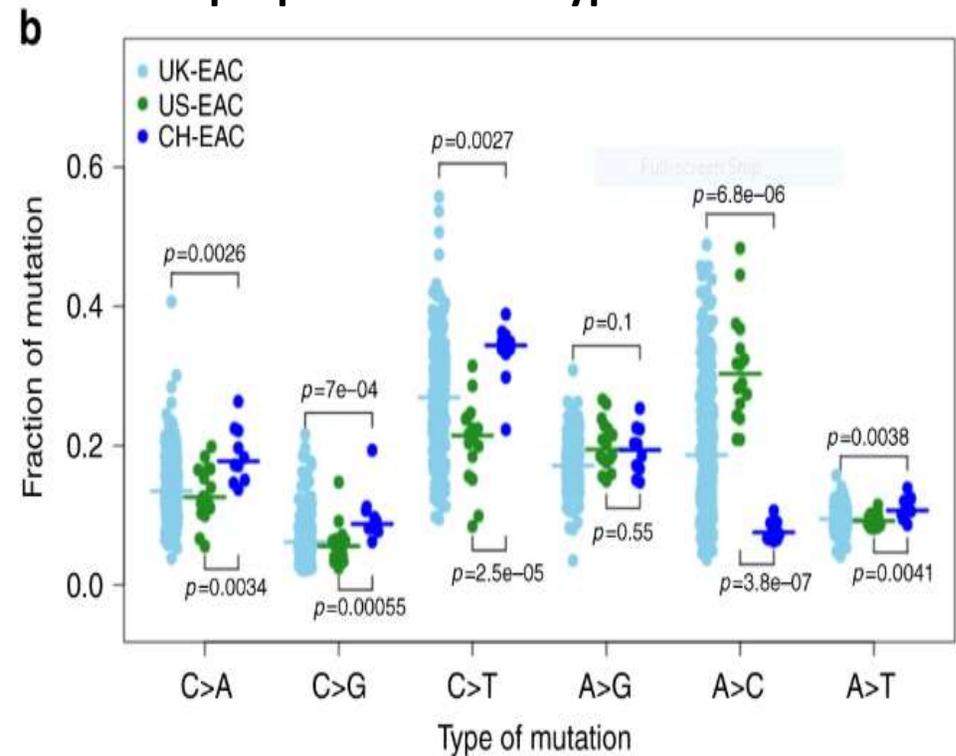
James Y. Dai^{1,2}, Xiaoyu Wang¹, Matthew F. Buas³, Chengjuan Zhang⁴, Jie Ma⁴, Bing Wei⁴, Yin Li⁵, Baosheng Zhao⁶, Teresa S. Hyun^{7,8}, Xueyan Chen⁹, Keith R. Loeb^{1,7,8,9}, Robert Odze¹⁰, Lena Yao¹¹, Xin Sun¹², Steve Self¹¹, Thomas L. Vaughan^{1,13} & Yongjun Guo⁴

From: Whole-genome sequencing of esophageal adenocarcinoma in Chinese patients reveals distinct mutational signatures and genomic alterations

The number of mutations per million base pairs

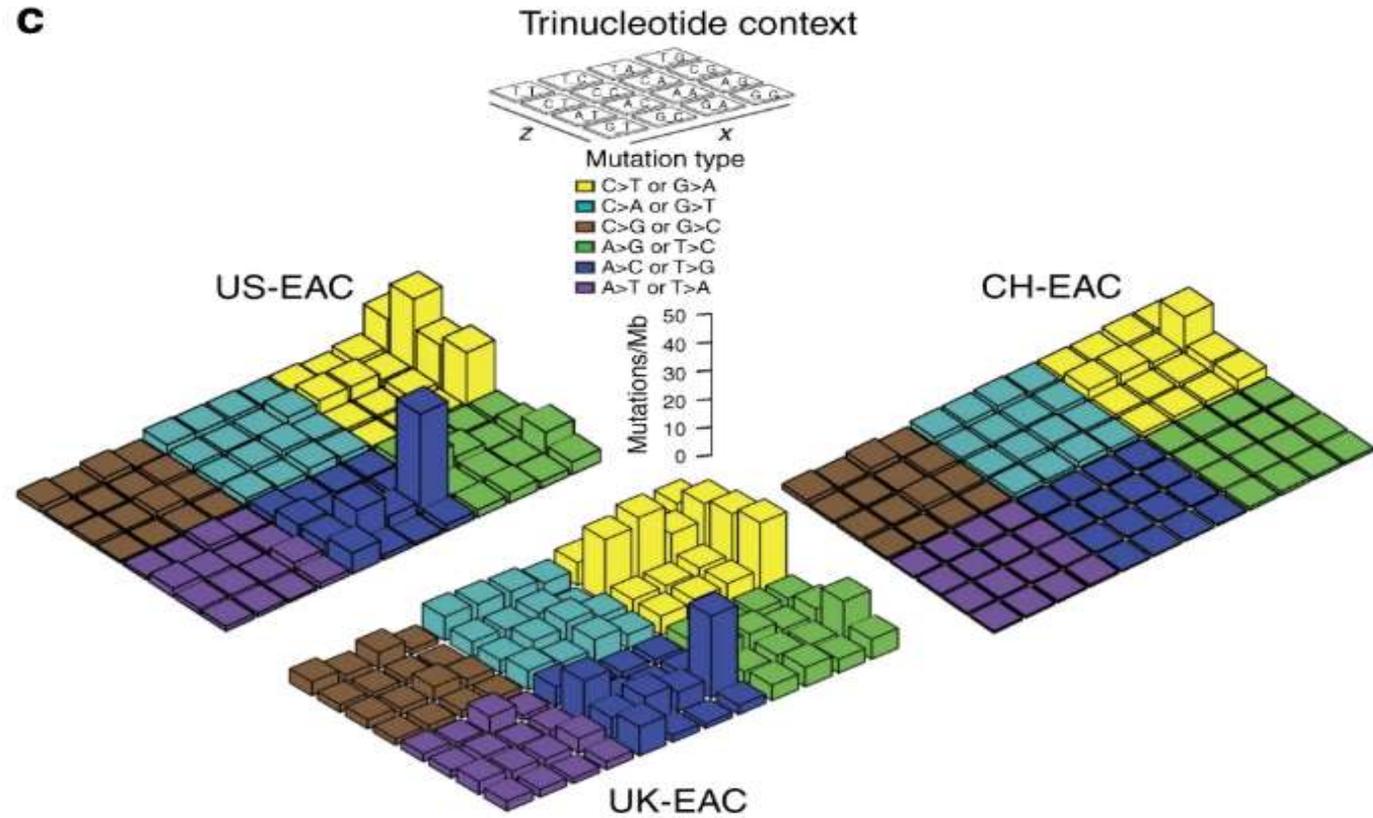


The proportion of six types of mutations



Mutation burden of six mutation types in the trinucleotide context

c



Recommendations in management of EAC

- Surgery
 - Chemotherapy
 - Chemoradiation
- neoadjuvant
- adjuvant
- **Targeted therapies** along with chemoradiation
 - anti-receptor tyrosine-protein kinase Erb-2 (HER2)
 - anti-Epidermal growth factor receptor (EGFR))
- *Limited success with average 5-year survival of <18%

Needs further extensive search for newer therapeutic agents

Conclusion

- Genetic abnormalities in EAC are linked to chronic inflammation and oxidative stress in response to acid reflux
- Genetic analysis of western EAC is showing some promising results for early diagnosis and identification of new therapeutic targets
- But there is little hope for Asian EAC

Conclusion

- **The overall prognosis of EC is poor worldwide as well as in Bangladesh**
- **We need to emphasize more on prevention rather than looking for newer promising cancer therapies in Bangladesh**



THANK YOU