Program on the Origins of Gastroesophageal Cancers

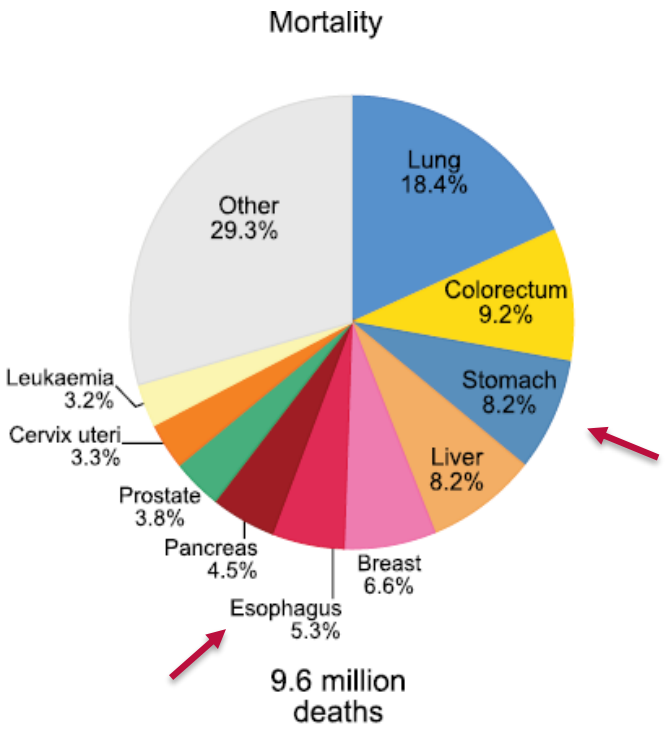
Rihab Yassin, PH.D.

Division of Cancer Biology

December 2, 2020

NIH NATIONAL CANCER INSTITUTE

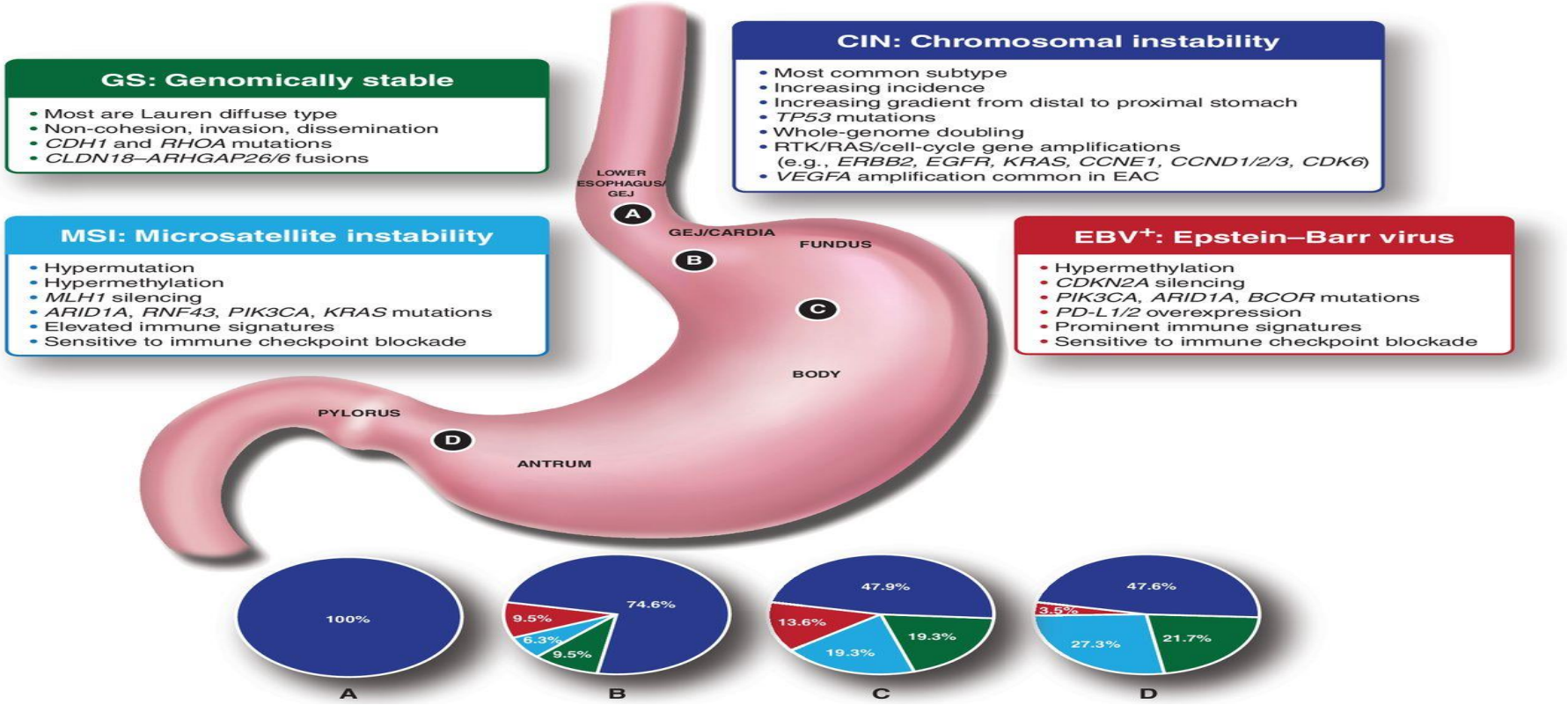
The Problem



GLOBOCAN 2018

- Gastroesophageal cancers are aggressive and lethal global cancers with poor survival.
- The incidence of distal stomach cancers (H. pylori) has significantly decreased in the USA/Western Europe.
- The incidence of proximal stomach, gastroesophageal junction, and lower esophagus cancers has reciprocally and significantly increased.
- Etiologic factors such as diet, gastroesophageal reflux disease (GERD) and obesity may underlie this increase.

A Decade of Genomics & Molecular Advances

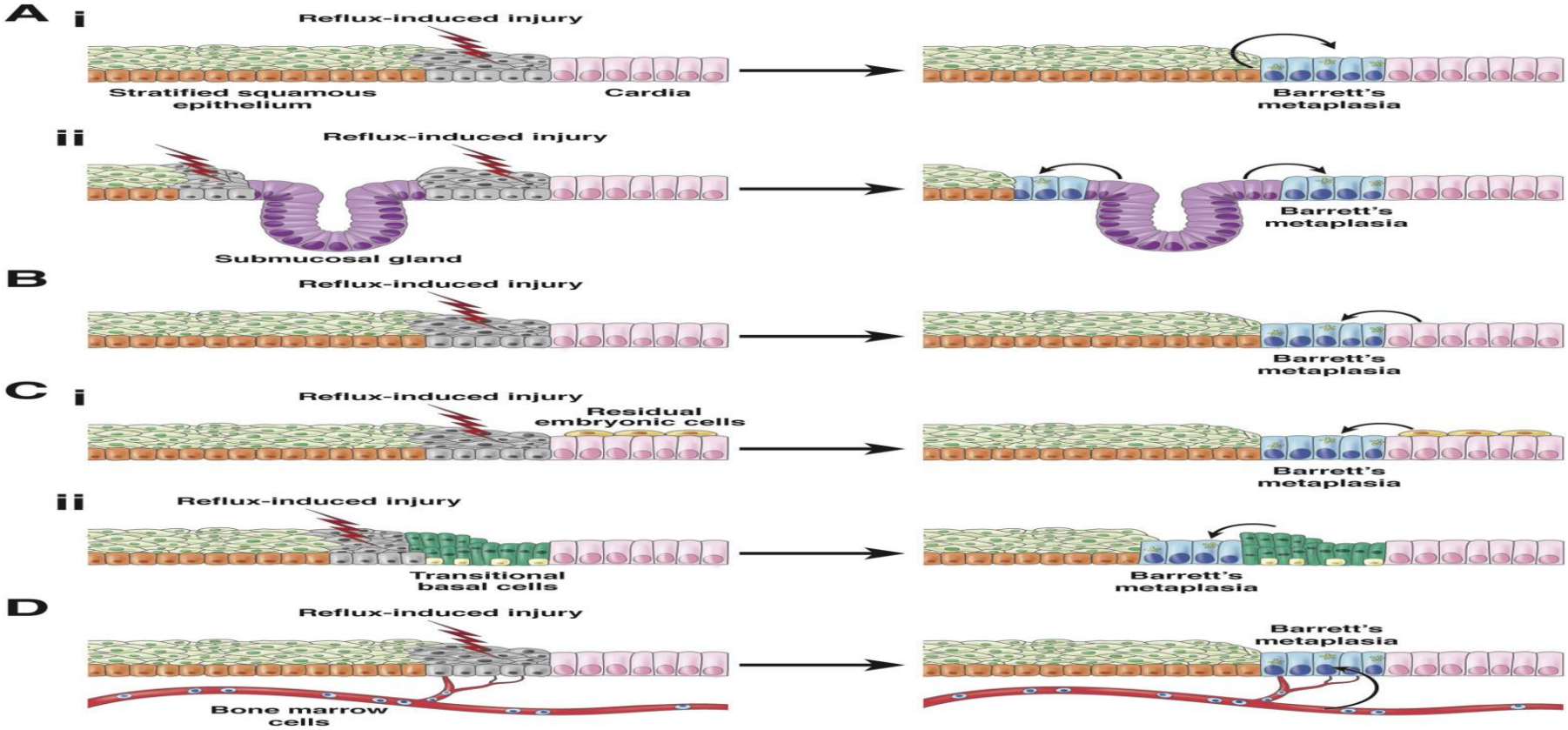


Cancer Discovery 2019 December; 9(12): 1656–1672. doi:10.1158/2159-8290.CD-19-0487

But Key Questions Remain

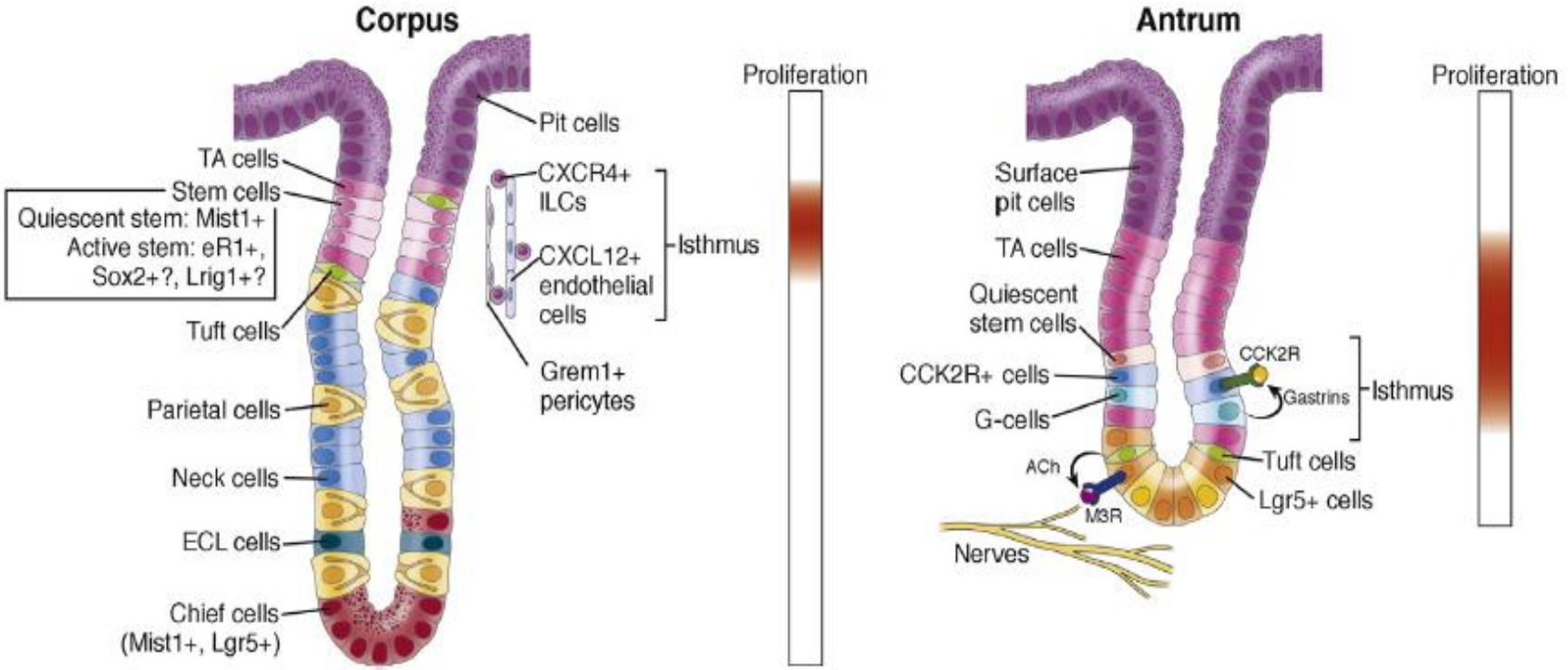
- How do these related cancers initially evolve?
- Do the genomics/molecular similarities point to similar evolution mechanisms?
- What are the mechanisms and effectors that direct the proliferation and expansion of gastroesophageal stem cells and their progeny; will the process be similar for different etiological contributors such as inflammation, acid, microbiota, and others?

Proposed Origins of Esophageal Cancer



Gastroenterology. 2019 August ; 157(2): 349–364.e1. doi:10.1053/j.gastro.2019.03.072

Proposed Origins of Gastric Cancer



Cell Mol Gastroenterol Hepatol 2017;3:331–338; http://dx.doi.org/10.1016/j.jcmgh.2017.01.013

Research is Positioned to Address the Origins of GE Cancers

- Current molecular classifications of gastric and junctional cancers.
- Recent understanding of their cancer genomics.
- Initial discoveries of gastric stem cells as a potential cell of origin for esophageal adenocarcinoma.
- Recent NCI-sponsored think tank on the origins of gastrointestinal cancers-highlighted the promising yet limited research area that could benefit from organized collaborations.
- The dismal cancers with cumulative 5-year relative survival of 21-31% only.

New NCI Program on the Origins of GE Cancers

- A program dedicated to the origins of upper gastric and junctional esophageal adenocarcinomas.
- Compare and contrast the contributions of inflammation, molecular events, and the cell of origin in driving early transformation.
- Attract investigators from outside fields to interject innovative ideas, models, and technological advances.
- Build a cadre of investigators, including new and early stage, who can function as a center to drive this research forward and overcome challenges and complexities.
- Chart the path for future investigations beyond gastroesophageal cancers.

Program on the Origins of GE Cancers

- **Research Projects (R01s; initially proposed as U01s)**

  Multi-Principal investigators with various research expertise to form:

  - A cohesive program that charts research advances on the origins of GE cancers
  - Community approach to testing research questions, sharing of knowledge, and solving problems/challenges

- **Coordinating Center (U24)**

  - Implements the framework for program coordination and facilitates resource generation and sharing across the program

- **NCI Program**

  - Program oversight; maximize collaborations; prioritize resource sharing

Program Research Focus

Examples

Fundamental Early Biology

- What are the mechanistic similarities and differences in the origins of gastric and junctional cancers; is the origin of different genomic types underlined by similar or different events.

- Are unique cell population(s) endowed with diverse functional properties to wound heal and initiate neoplastic changes; are these cellular functions distinct and pre-determined in a hierarchical order or according to niche associated factors.

- Do cell lineages interconvert beyond boundaries in homeostasis, during wounding/repair/regeneration, or only upon attrition of genetic and epigenetic controls; are there distinct plasticity programs driving lineage switching.

Gender Disparity

- Can gender-specific factors such as those encoded by the Y or X chromosomes be defined that may interact with inflammation/environmental effectors to promote early transformation.

Research Focus (Continued)

Racial/Ethnics Factors

- How would biological mechanisms in certain racial/ethnic populations affect the stem cell state and work with inflammation to initiate transformation.

- Can susceptibility or protective factors be defined in the gastroesophageal mucosa of racial/ethnic populations that may impact the injury and repair processes and the origins of these cancers.

Models

- Can innovative and tractable models be developed to understand the early transformation of human epithelium.

Long-Term Impact

- Provide an unprecedented opportunities to understand the earliest changes in transformation preceding any histological manifestation or neoplasia.

Portfolio Analysis-Current Active Grants

- **8 Extramural grants with a cell of origin component or aim:**
  - Majority are “R” grant mechanisms.
  - Almost equally distributed between stomach and esophagus.

Program Proposed Budget

Grant Mechanism	1 Year Cost	5 Year Cost
R01 Project Grants (5-6)	$3,500,000	$17,500,000
U24 Coordinating Center (1)	$500,000	$2,500,000
Total Direct Cost	$4,000,000	$20,000,000
Total Cost	$6,600,000	$33,000,000

Program Evaluation Principles

- Collaborations between the grant projects.
- Recruitment and training of early career investigators.
- Publication of key research findings.
- Publication of a white paper that critically reviews the field-outlines available opportunities/challenges for the wider research community.
- Development and sharing of models and resources to address challenging questions regarding the origins of gastric and junctional cancers.
- Active participation and progress discussion at the annual investigators and other meetings.
- Investigators participation in development of new projects and funding.
- Participation in national conferences with leaders from the extramural community.

Acknowledgments

- BSA Subcommittee Members:
  - Dr. David Tuveson (Chair)
  - Dr. Christopher Counter
  - Dr. W. Kimryn Rathmell

QUESTION?

www.cancer.gov

www.cancer.gov/espanol