Gastric and Esophageal Cancers Working Group Report

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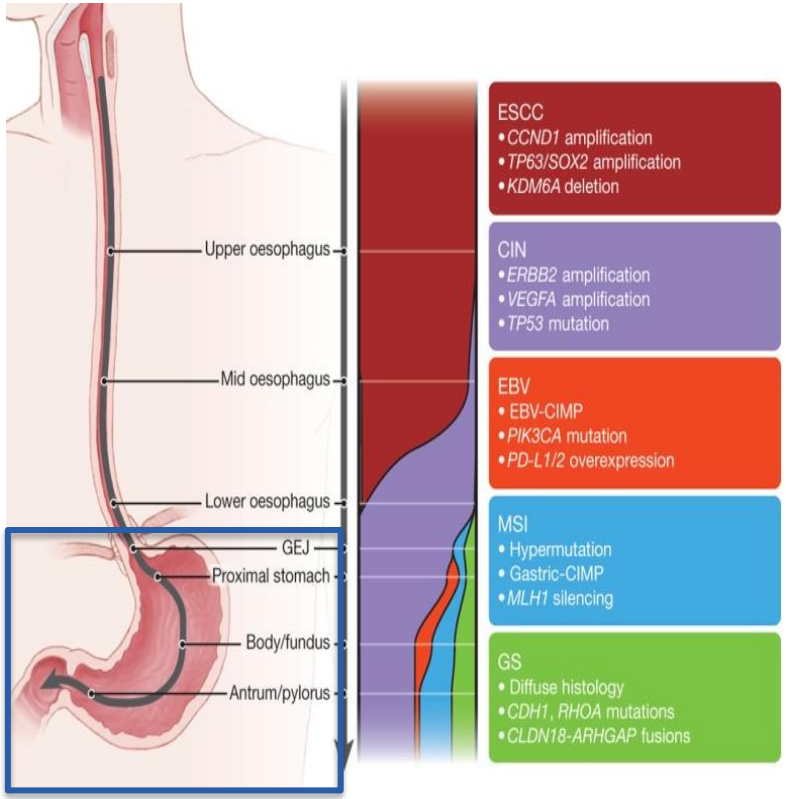
Presentation to CTAC
November 9, 2022

Outline

- Brief overview of the epidemiology
- Working Group background and process
- Recommendations
  - Overarching research strategy
  - Specific recommendations
- Conclusions

Gastric Cancer

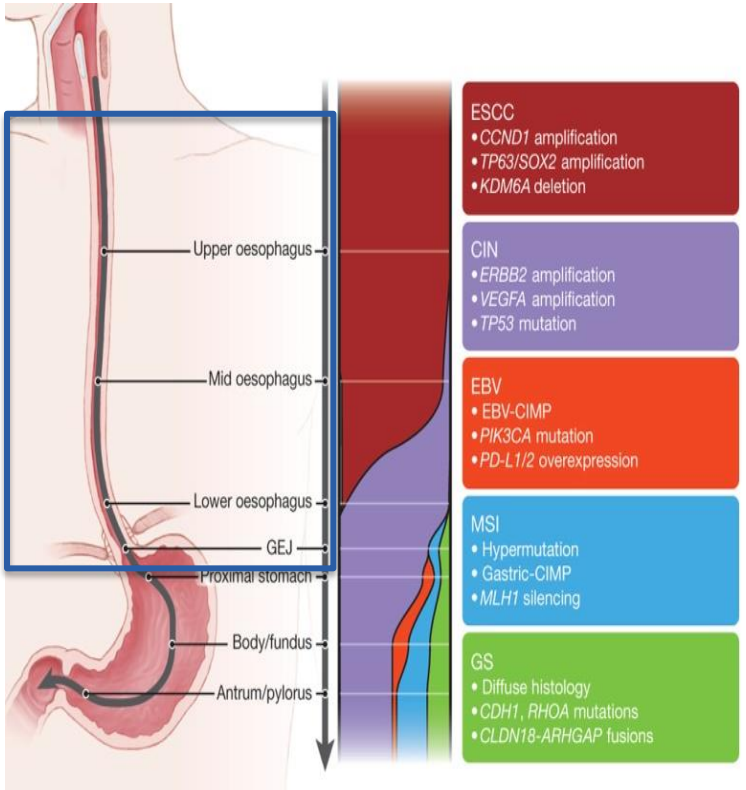
- Gastric adenocarcinoma accounts for about 95% of stomach cancers
- ~10% associated with hereditary syndromes
- Other risk factors include *H. pylori* or EBV infection, diet, smoking, pernicious anemia, family history
- Classifications: anatomic, histologic, and molecular subtypes
- Declining overall incidence and mortality, but 5-year survival rate remains low (33.3%)
  - Incidence is increasing in young, non-Hispanic White females



J Kim *et al. Nature*, 2017

Esophageal Cancer – Two Major Types

- Squamous cell carcinoma (ESSC)
  - Associated with tobacco and alcohol
  - Higher incidence in males and Blacks
  - More frequent in middle or upper esophagus
  - Incidence declining in the US
- Adenocarcinoma (EAC)
  - Associated with obesity and chronic reflux
  - More frequent in distal esophagus
  - Usually develops from Barrett's esophagus
  - Incidence increasing; now predominant type in US
- Overall, modest decline in mortality over time, but 5-year survival remains low (20.6%)



J Kim *et al. Nature*, 2017

Rationale for Working Group

- Gastric and esophageal cancers are lethal and have poor survival
- Language accompanying FY20 Appropriations directed NCI to develop a scientific framework for the prevention, diagnosis, and treatment of these cancers
- NCI sought advice from the Working Group to help identify the most impactful ***translational research*** questions to advance the prevention, diagnosis, and treatment of gastric and esophageal cancers

G&E Cancers Working Group Membership

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Working Group Mission and Scope

- **Mission – Survey the scientific horizons broadly to identify:**
  - Translational research knowledge gaps related to gastric and esophageal cancer
  - The most provocative and impactful translational research questions to advance the prevention, diagnosis, and treatment of gastric and esophageal cancer
  - The most important opportunities for application of new technologies to gastric and esophageal cancer translational research
- **Scope**
  - Focus on most common forms of "gastroesophageal cancer"
    - Gastric adenocarcinoma and the two major types of esophageal cancer (adenocarcinoma and squamous cell carcinoma)

Working Group Activities & Timeline

- December 13, 2021 – initial virtual plenary meeting
  - Charge from Dr. Ned Sharpless
  - Review NCI grant and clinical trials portfolios for gastric and esophageal cancer
- Spring 2022 – subgroup discussions
- June 29, 2022 – second virtual plenary meeting
- August – October 2022 – report drafting
- November 9, 2022 – presentation of report to CTAC

Working Group Subgroups

- **“-Omic” technologies**, including functional genomics, transcriptomics, proteomics, metabolomics, microbiomics, etc. (Lead: Sandy Markowitz)
- **Experimental model systems**, including mouse, 2D and 3D organoids, patient-derived xenografts, human tissues, and animal/human imaging (Lead: Rick Peek)
- **Prevention, screening, surveillance, and early detection** (Lead: Marcia Cruz-Correa)
- **Treatment, correlative studies, and additional enabling technologies** including big data, radiomics, and biobanking (Lead: Syma Iqbal)

Recommendations

Overarching Research Strategy: Rationale (1)

- Working Group consensus regarding current landscape:
  - Available targeted and immunotherapeutic agents have had modest impact so far in treatment of G & E cancers
  - Cost and invasiveness of existing assessment modalities limits population-level screening, detection, and surveillance
  - Progress on prevention limited by absence of practical concepts for preventive interventions other than for *H. pylori* infection

Overarching Research Strategy: Rationale (2)

- Working Group concluded:
  - Research strategy should focus on building a more robust pipeline of translational opportunities
  - Research strategy should address both enabling resources and substantive goals
    - Strengthen key enabling resources and tools
    - Apply enhanced resources and tools to identify new markers, targets, interventions, and population strategies with sufficient promise to justify focused translational efforts

Overarching Research Strategy

Develop precision approaches for the prevention, screening, detection, surveillance, and treatment of gastric and esophageal cancers by:

- **Building repositories of well-characterized biospecimens and model systems** that embody key stages in gastric and esophageal carcinogenesis and progression across diverse populations
- **Further developing analytic tools and computational methods** to characterize gastric and esophageal cancer pathophysiologic processes with greater clarity and insight
- **Identifying actionable markers and targets** within the processes of gastric and esophageal carcinogenesis and progression
- **Developing novel clinical assessment tools and interventions** for gastric and esophageal cancers based on those markers and targets

Specific Recommendations

- Enabling Resources
  - Biospecimen Repositories
  - Research Tools
- Future Research Directions
  - Biological Insights and Fundamental Research
  - Treatment
  - Prevention

Enabling Resources: Biospecimen Repositories

Biospecimen Repositories: Rationale

- Clinically-annotated biospecimens with defined, disease-related characteristics are a critical enabling resource for the research needed to identify markers and targets specific to gastric and esophageal cancer
- Collection strategies of existing general biorepositories not focused on gastric and esophageal cancer have achieved modest representation of tissues from gastroesophageal cancers, with a haphazard mix of attributes
- Access hurdles for researchers who wish to make use of specimens from the repositories further limit the impact of these resources

Biospecimen Repositories: High-Level Recommendations

- **Recommendation BR-1:** Launch a concerted effort to overcome logistical obstacles and **assemble repositories of clinically annotated biospecimens** that embody key stages in gastric and esophageal carcinogenesis and progression across diverse populations

- **Recommendation BR-2: Identify an initial set of high-priority biospecimens** to be made available through a national repository that is accessible to all qualified researchers with meritorious proposals

Biospecimen Repositories: Sub-Recommendations

- **Recommendation BR-S1: Collect specimens** from both observational and interventional study cohorts that illuminate key events in carcinogenesis and progression as well as variations in these processes across populations
- **Recommendation BR-S2: Create observational and interventional study cohorts that enable efficient collection** of specimens with desired characteristics
- **Recommendation BR-S3: Promulgate standards** for collection, processing and characterization of tissue specimens needed for different analyses

Enabling Resources: Research Tools

Research Tools: Rationale

- Emerging methods in three domains – model systems, laboratory analytic methods, and computational methods – applied individually and in combination offer great potential to generate novel fundamental insights and facilitate identification of actionable markers and intervention targets
- Each approach requires further development to achieve its full potential

Research Tools: High-Level Recommendation

- **Recommendation RT-1: Develop and refine research tools** to further enhance our ability to derive insight into the biology of gastric and esophageal cancer from patients, biospecimens, and model systems

- Sub-recommendations related to:
  - Model Systems
  - Laboratory Analytic Methods
  - Computational Methods

Research Tools: Sub-Recommendations on Model Systems

- **Recommendation RT-MS1:** Develop preclinical and animal **models that more faithfully recapitulate GE carcinogenesis and progression** in humans and that represent diverse populations and prioritized questions
- **Recommendation RT-MS2:** Collaborate with bioengineers, medical physicists, and other specialists to develop **model systems with greater complexity and biological realism** for G & E cancers
- **Recommendation RT-MS3:** Collaborate with bioengineers, chemical engineers, and others to develop **more economical synthetic reagents and culture systems and more efficient ways to replicate and distribute model systems**
- **Recommendation RT-MS4: Promulgate standardized methods** for generating and replicating uniform, well-characterized model systems

Research Tools: Sub-Recommendation on Laboratory Analytic Methods

- **Recommendation RT-AM1: Develop and refine biological, chemical, and physical analytic methods**, including incorporation of the spatial domain, to complement the growing variety of -omics tools and further enhance our ability to derive insight into the biology of gastric and esophageal cancer from patients, biospecimens, and model systems

Research Tools: Sub-Recommendation on Computational Methods

- **Recommendation RT-CM1:** Collaborate with bioengineers, medical physicists, bioinformatics specialists, and other disciplines to **develop and validate machine learning approaches** for assessing patterns within and across diverse -omics and other data types **to infer interventional targets** for prevention or treatment of gastric and esophageal cancer

Future Research Directions: Biological Insights and Fundamental Research

Biological Insights and Fundamental Research: Rationale

- The goal is to “harvest” the many ongoing advances in research methods by applying them to biological questions specific to gastric and esophageal cancer, in order to build a more robust pipeline of translational opportunities
- Working Group acknowledges and seeks to build on NCI’s new program dedicated to the origins of gastric and junctional esophageal adenocarcinomas (RFA-CA-21-026/RFA-CA-21-027)

Biological Insights and Fundamental Research: High-Level Recommendation

- **Recommendation BI-1: Apply -omics and other emerging analytical tools and computational methods** to characterize gastric and esophageal cancer pathophysiologic processes with greater clarity and insight and **identify translationally actionable markers and targets** within the processes of gastroesophageal carcinogenesis and progression

Biological Insights and Fundamental Research: Sub-Recommendations

- **Recommendation BI-S1: Improve molecular characterization of G&E precancer and disease progression** from emergence of precancer through early-stage cancer to disease recurrence and advanced disease, **across diverse racial/ethnic populations**, hereditary risk groups and cancer subtypes. Seek an integrated understanding of how genomic, molecular, clinical, environmental, and behavioral factors interact to determine risk of G&E cancer initiation and progression
- **Recommendation BI-S2: Elucidate the functional significance** for gastric and esophageal cancer **of genomics, proteomics, metabolomics, microbiomics, and tumor microenvironment** and characterize associated targets that may be susceptible to intervention
- **Recommendation BI-S3: Investigate the biology of exceptional responders** in gastric and esophageal cancer **and of acquired and *de novo* resistance** to immunotherapies and targeted therapies

Future Research Directions: Treatment

Treatment Research: Rationale

- Surgical resection is potentially curative for the few patients with localized disease
- Current chemotherapy regimens yield limited survival
- With the modest exception of trastuzumab in HER2-positive tumors, targeted therapies have been disappointing to date
- Immunotherapies show promise, though many tumors are immunologically "cold"
- Research is needed to identify immune targets, novel treatment combinations, and patients that will respond best to specific treatments

Treatment Research: High-Level Recommendation

- **Recommendation T1:** Apply -omics and other emerging analytical tools and computational methods to **translate emerging biological insights** on gastric and esophageal cancer **into improved clinical assessment tools and therapeutic regimens**, tailored more effectively to the distinctive characteristics of each patient's disease process

- Sub-recommendations related to:
  - Clinical Assessment Tools
  - Therapeutic Regimens

Treatment Research: Sub-Recommendations on Clinical Assessment Tools

- **Recommendation T-S1: Develop improved methods for predicting and monitoring response and resistance** of gastric and esophageal cancer to therapy, particularly for guiding treatment of patients receiving front-line therapy and immunotherapy combinations
- **Recommendation T-S2: Develop surrogate markers of therapeutic effect** in gastric and esophageal cancer to enable rapid assessment of new agents and accelerate clinical trials

Treatment Research: Sub-Recommendations on Therapeutic Regimens

- **Recommendation T-S3: Develop improved treatments** for gastric and esophageal cancer, particularly for patients with refractory disease, including optimized and novel:
  - Immunotherapy and immune-oncology combination regimens
  - Targeted therapies
  - Cell-based therapies
- **Recommendation T-S4: Identify targets and develop methods for image-guided treatment** in gastric and esophageal cancer
- **Recommendation T-S5: Develop new approaches to preventing or mitigating adverse effects** associated with gastric and esophageal cancer and/or its treatment

Future Research Directions: Prevention

Prevention Research: Rationale

- Screening and surveillance pose an especially difficult challenge: modalities for use in population-scale programs must not only be technologically feasible but also logistically and economically practical
- The complexity of *H. pylori* epidemiology and pathophysiology require a broad-based approach addressing both vaccines and other interventions as well as strategies for optimal matching of interventions with patients and populations
- Preventive interventions are needed for non-*H. pylori*-related gastric and esophageal cancers as well

Prevention Research: High-Level Recommendation

- **Recommendation P1:** Apply -omics and other emerging analytical tools and computational methods to **translate emerging biological insights into improved practical tools and strategies for risk stratification, screening, early detection, and surveillance** of both precancerous lesions and gastric and esophageal cancers, as well as practical and effective preventive interventions tailored to the characteristics of specific populations
- Sub-recommendations related to:
  - Screening, Detection, and Surveillance
  - Preventive Interventions

Prevention Research: Sub-Recommendations on Screening, Detection, and Surveillance

- **Recommendation P-S1: Develop more sensitive and accurate assessment tools for screening and early detection** of gastric and esophageal cancer
- **Recommendation P-S2: Develop more sensitive and accurate assessment tools to characterize gastric and esophageal cancer risk**. Evaluate the use of endoscopy findings, including innovative molecular probes and AI/machine learning approaches, as a risk stratifier
- **Recommendation P-S3: Develop more sensitive and accurate assessment tools for gastric and esophageal cancer disease surveillance**

Prevention Research: Sub-Recommendations on Preventive Interventions

- **Recommendation P-S4: Develop novel preventive interventions** for gastric and esophageal cancer
- **Recommendation P-S5:** Apply state-of-the-art vaccine development technologies to **advance the development of *H. pylori* vaccines**
- **Recommendation P-S6: Define optimal antibiotic stewardship practices for *H. pylori* eradication**, including surveillance systems for antibiotic resistance

Conclusions (1)

- The epidemiologic and clinical realities of gastric and esophageal cancer define a compelling need for substantial advances in prevention, detection, surveillance and treatment
- Reviewing two decades of progress, the Working Group concluded that a concerted and sustained effort is needed to build a more robust pipeline of translational opportunities

Conclusions (2)

- No one intervention or priority will serve as a panacea. Instead, the Working Group recommends a broad-based, interdisciplinary approach spanning prevention, screening/ surveillance/early detection, risk, and therapy
- The Working Group identified dedicated biospecimen and model system resources as critical to this effort
- This broad-based approach requires a focus on collaborations between federal agencies, public and private universities/institutes, industry, patient advocates, and philanthropy

Questions?