AGENDA

01 EPIDEMIOLOGY
The epidemiology of EOCRC globally and in the United States.

02 EXPOSOME
Exposures or risk factors potentially contributing to the rising risk of EOCRC.

03 GENETICS & EPIGENETICS
Molecular aspects of EOCRC.

04 CONCLUSION
Remarks and recommendations
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Global Prevalence

Incidence rates adjusted to the 1960 Segi world standard population.
EOCRC incidence increased in 19 countries. Nine of which had stable or declining trends in older adults.
Increasing incidence rates across birth cohorts
US Incidence

**Incidence of EOCRC**
Incidence rate of EOCRC raised by more than 50% in both genders since 1994.

**Incidence of LOCRC**
Incidence rate of LOCRC declined by around 34% in both genders since 2000.
US Mortality

Mortality of EOCRC
Mortality rate of EOCRC raised by around 13% in both genders.

Mortality of LOCRC
Mortality rate of ILOCRC declined by around 34% in both genders.
140% Rise in EOCRC is expected by 2030.

Leading to increase of EOCRC accounted cases in CRC from 10% for 25%.

EOCRC Incidence

Murphy et al. 2018
EOCRC Age Distribution

44% of EOCRC cases are 45-49 years old
EOCRC by Race/Ethnicity

- NH White: APC, +2.0
- Am Indian/ AK Native: APC, +2.2
- NH Black: APC, +0.5
- Asian/ Pacific Islander: APC, +0.4
- Hispanic: APC, +2.8

Annual per cent change (APC) Bold = p<0.05
EOCRC per State for NHW

42/47 States had rise in EOCRC cases

Average Annual per cent change (AAPC) from 2006-2015

Siegel RL, et al. JNCI' 2019
EOCRC Subsite

40% of EOCRC cases are rectal cancer

Slide from Siegel RL, 2020
EOCRC Clinical Diagnosis

**Stage**
Diagnosed at stage III or IV.

71%

**Family**
Around 80% with young children

80%

**Diagnosis Time**
Visited two physician at least before they get the diagnosis.

67%

**Diagnosis Period**
Waited six months at least when they experienced symptoms before talking to a doctor

41%
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## Specific External Environment

<table>
<thead>
<tr>
<th>Etiological factors</th>
<th>Level of evidence</th>
<th>Unit increase</th>
<th>RR (95% CI)</th>
<th>Temporal trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>++</td>
<td>5 kg/m² in BMI</td>
<td>1.05 (1.03–1.07)</td>
<td></td>
</tr>
<tr>
<td>Western dietary pattern</td>
<td>++</td>
<td>Highest vs lowest</td>
<td>1.12 (1.01–1.24)</td>
<td>Poorest in 2000s then stable</td>
</tr>
<tr>
<td>Processed meat</td>
<td>++</td>
<td>50 g per day</td>
<td>1.16 (1.08–1.26)</td>
<td></td>
</tr>
<tr>
<td>Alcohol (as ethanol)</td>
<td>++</td>
<td>10 g per day</td>
<td>1.07 (1.05–1.09)</td>
<td>Peak in 1980s then</td>
</tr>
<tr>
<td>Red meat</td>
<td>+</td>
<td>100 g per day</td>
<td>1.12 (1.00–1.25)</td>
<td>Peak in 1970s then</td>
</tr>
<tr>
<td>Diabetes</td>
<td>+</td>
<td>Yes vs no</td>
<td>1.30 (1.20–1.40)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>+</td>
<td>Current vs never</td>
<td>1.15 (1.00–1.32)</td>
<td></td>
</tr>
<tr>
<td>Total physical activity</td>
<td>–</td>
<td>5 MET - hours per week</td>
<td>0.97 (0.94–0.99)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>–</td>
<td>75-1200 mg per day</td>
<td>0.76 (0.63–0.94)</td>
<td></td>
</tr>
<tr>
<td>Total fiber</td>
<td>–</td>
<td>10 g per day</td>
<td>0.93 (0.87–1.00)</td>
<td></td>
</tr>
<tr>
<td>Whole grain</td>
<td>–</td>
<td>90 g per day</td>
<td>0.83 (0.79–0.89)</td>
<td></td>
</tr>
<tr>
<td>Total calcium</td>
<td>–</td>
<td>300 mg per day</td>
<td>0.92 (0.89–0.95)</td>
<td></td>
</tr>
</tbody>
</table>

Exposome to Microbiome

Early-life exposures
- Mode of nutritional provision
  - Breastfeeding
  - Diet formula
  - Pre-probiotic supplement
- Mode of delivery
  - Caesarean
  - Vaginal
- Environment
  - Psychological and/or physical stress
- Family environment and pets
- Genetics
- Antibiotics
  - 2.7 courses by age 2 years
  - 10.9 courses by age 10 years
- Maternal infection, disease and/or medication
- Maternal nutrition
- Maternal stress

Exposomal elements
- Global westernization of diet
- Unhealthy cooking practices
- Red and processed meats
- Synthetic dyes
- MSG
- Titanium dioxide
- High-fructose corn syrup

Microbiome development

Infancy  Childhood  Adulthood

Immunity and/or inflammation
- Obesity
- Diabetes

EOCRC
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Genetic Susceptibility

The Genes, Environment, and Health Initiative

Genetic Susceptibility - Linking Exposure to Disease

Exposure Biology Program

- Identify genetic variants in animal models, develop technology and biomarkers
- Diet
- Physical Activity
- Environmental Exposures
- Psychosocial Stress and Addictive Substances

Human Genetics Program

- GWA Studies
- Data Analysis
- Replication
- Sequencing
- Database
- Function
- Translation

GxE

Time

NIH, NIEHS
Genes of EOCRC

~70-80% unknown
Polygenic Risk Score

CRC-associated common genetic variants to associate with EOCRC

Risk estimates for early-onset vs. late-onset CRC associated with a 95-SNP PRS\(^1\)

<table>
<thead>
<tr>
<th>PRS</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 Years-Old</td>
<td>1.73 (1.17, 2.56)</td>
<td>0.0056</td>
</tr>
<tr>
<td>≥50 Years-Old</td>
<td>1.43 (1.34, 1.51)</td>
<td>2.77E-31</td>
</tr>
<tr>
<td>Negative Family History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 Years-Old</td>
<td>1.76 (1.11, 2.78)</td>
<td>0.0161</td>
</tr>
<tr>
<td>≥50 Years-Old</td>
<td>1.42 (1.33, 1.52)</td>
<td>2.85E-25</td>
</tr>
<tr>
<td>Positive Family History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 Years-Old</td>
<td>1.56 (0.75, 3.26)</td>
<td>0.2334</td>
</tr>
<tr>
<td>≥50 Years-Old</td>
<td>1.34 (1.17, 1.54)</td>
<td>2.87E-05</td>
</tr>
</tbody>
</table>

\(^1\)Cox models include sex, principal components, and continuous PRS

Archambault A. et al, Gastroenterology’ 2020
Early-Onset Colorectal Cancer Group

Colorectal Cancer
Moon Shot Research
Among 1500+ New Patients with CRC seen in the MDACC GI Center each year, about 1 in 3, were between ages of 18-50.
### MDACC Dataset + AACR GENIE

<table>
<thead>
<tr>
<th>Patient Information</th>
<th>MDACC Molecular Cohort</th>
<th>MDACC Tumor Registry Cohort</th>
<th>AACR Project GENIE Cohort</th>
<th>CMS Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1877</td>
<td>N=32597</td>
<td>N=1868</td>
<td>Total N=626</td>
</tr>
<tr>
<td></td>
<td>Seen at MDACC from January 1, 2012 to September 1, 2016</td>
<td>Seen at MDACC from January 1, 1980 to present</td>
<td>Excluded patients from MDACC to prevent duplication of data</td>
<td>N=448 from TCGA N=178 from MDACC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>Baseline clinical and pathologic characteristics</th>
<th>Baseline clinical and pathologic characteristics</th>
<th>Limited clinical and pathologic characteristics</th>
<th>Limited clinical and pathologic characteristics</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Molecular Data</th>
<th>Mutational data available from 46- or 50-gene CLIA next-generation sequencing panel</th>
<th>Unavailable</th>
<th>Mutation data available from AACR Project GENIE database, which includes a mixture of next-generation sequencing platforms</th>
<th>RNA expression data. For TCGA patients, data were publicly available. For MDACC patients, data were obtained with Affymetrix RNA expression arrays.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cancer Stage(s)</th>
<th>Stage IV</th>
<th>Stages I-IV</th>
<th>Majority stage IV</th>
<th>Stages I-IV</th>
</tr>
</thead>
</table>

| Additional Data | Comorbid predisposing condition information available for patients < 50 years | | Classification by CMS subtype | |

#### Foundation Medicine

18,218 total patients
- 1,420 patients under the age of 40
- 3,248 between 40 and 49
- 13,550 age 50 and older
No significant difference in \textit{KRAS, NRAS} mutations

Willauer et al. Cancer '19, Lieu CCR '2
Key reproducible finding of lower APC mutations

If not APC, CTNNB1 mutations, what alternative Wnt activating mechanisms exist?
Mechanisms of Wnt activation in CRC

**A**
- LRP5/6
- ZNRF3/RNF43
- WNT
- SFRP
- DKK1
- FZD
- LGR
- APC
- CK1
- AXIN
- GSK3
- β-catenin
- TCF/LEF

**B**
- LRP5/6
- ZNRF3/RNF43
- WNT
- FZD
- RSPO
- LGR
- APC
- CK1
- AXIN
- GSK3
- β-catenin
- TCF/LEF

**Legend**
- Phosphorylation
- Ubiquitination
Slight increase in \textit{CTNNB1} mutations

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{CTNNB1_mutation_prevalence}
\caption{Mutation Prevalence of CTNNB1 over time.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{CTNNB1 alteration rate vs age}
\caption{Alteration rate of CTNNB1 with age.}
\end{figure}

2.7\% $\rightarrow$ 4\%
RNF43 G659fs* mutations in early onset?
Likely nonfunctional

“These findings suggest that the frequent occurrence of RNF43-G659Vfs*41 may result from error-prone replication of the 7-G repeat in MLH1-deficient tumors and that the mutation itself does not inactivate the enzyme.”

Lieu CCR ‘19; Tu et al Sci Rep ‘19
Beyond Mutations: How do CRC differ by gene expression?

Grouping ~4,000 patient tumors by RNA profiling:

Each dot is one patient

Consensus Molecular Subtypes (CMS)

Guinney et al, Nat Med ‘15
## Key Features of the CMS Subtypes

<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSI Immune</strong></td>
<td><strong>Canonical</strong></td>
<td><strong>Metabolic</strong></td>
<td><strong>Mesenchymal</strong></td>
</tr>
<tr>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
</tbody>
</table>

- **MSI, CIMP high**
- **Hypermutation**
- **SCNA high**
- **Mixed MSI status**
- **SCNA low, CIMP low**
- **SCN high**

### BRAF mutations
- Immune infiltration and activation
- WNT and MYC activation
- Better survival after relapse

### KRAS mutations
- Metabolic deregulation
- Stromal infiltration
- TGF beta activation
- Angiogenesis

- Worse survival after relapse
- Worse relapse-free and overall survival
Higher CMS1 and CMS3 in EOCRC

TABLE 1. Baseline Characteristics of the MDACC Molecular Cohort Classified by Age

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>18-29 y</th>
<th>30-39 y</th>
<th>40-49 y</th>
<th>50-59 y</th>
<th>60-69 y</th>
<th>&gt;70 y</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No. (%)</td>
<td>46 (2)</td>
<td>177 (9)</td>
<td>411 (22)</td>
<td>605 (32)</td>
<td>454 (24)</td>
<td>184 (10)</td>
<td></td>
</tr>
<tr>
<td>MSI-H (n = 1525, 81% known), No. (%)</td>
<td>3 (7)</td>
<td>12 (8)</td>
<td>23 (3)</td>
<td>11 (2)</td>
<td>13 (4)</td>
<td>6 (4)</td>
<td>.038</td>
</tr>
</tbody>
</table>

Low rates of MSI-H
CMS1: Lack of usual associations with BRAF
CMS1: Lack of usual associations with right sided disease

Disconnect between tumor location, MSI-H status, and BRAF V600E mutation, which usually define CMS1.
CMS3: Modest association with diabetes and obesity
Overall survival and progression-free survival from diagnosis of mCRC is worse for EOCRC patients

20,003 patients from 24 first line studies of mCRC (ARCAD database)
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Conclusion

- EOCRC is a global phenomena with district molecular and anatomical features from LOCRC
- Prognosis with standard of care therapy is poor, despite aggressive utilization of chemotherapy and higher utilization of surgical resection
- The gut microbiota is probably at the links of these exposome and EOCRC
- Subtle findings in mutation profiles reiterate differences in biology
What We Need to Do?

01  Etiology  
unknown to the majority of ~ 80%

02  Risk Factor  
No known major risk factor

03  Mechanism  
No known differences in driver mechanisms

04  Evolution  
Unknown in EOCRC

Multi-omics