Why Young-Onset Colorectal Cancer: Modifiable risk factors

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Washington University in St. Louis
Disclosures

I have the following relevant financial relationships to disclose:

- Consultant for: Geneoscopy
Outline

• Evolving epidemiology of colorectal cancer (CRC)
• Modifiable risk factors of early-onset CRC
The decline in CRC incidence slowed down from 3%-4% annually during the 2000s to 1% annually during 2011–2019.

Driven partly by an increase in <55 y of 1%-2% annually since the mid-1990s.

<55 y
- 1995: 11%
- 2019: 20%

Siegel et al. CA Cancer J Clin, 2023
EO-CRC in the US
Higher incidence in successive birth cohorts

Birth cohort effects

Median age of CRC diagnosis

Siegel et al, J Natl Cancer Inst, 2017
Siegel et al, CA Cancer J Clin, 2020
Cao lab@Washington University in St Louis  
EO-CRC/EO-adenoma, 2017+

<table>
<thead>
<tr>
<th>Prospective cohorts</th>
<th>Real-world evidence</th>
<th>Genetic consortium</th>
<th>Microsimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2017-2023</strong></td>
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</tbody>
</table>

**Emerging risk factors throughout the life course**
- Obesity (life course), *JAMA Oncology* 2018
- Sedentary behavior
  - *JNCI Cancer Spectrum* 2019
  - *JAMA* 2019
- Metabolic syndrome, *Gut* 2020
- Diet quality, *JNCI* 2020
- Diabetes, *Gastro Hep Advances*, 2021
- Sugar-sweetened beverages (life course), *Gut* 2021
- Sulfur microbial diet, *Gastroenterology* 2021
- Vitamin D, *Gastroenterology* 2021
- Cesarean delivery, *JAMA Network Open* 2023
- Earlier signs and symptoms, *JNCI* 2023
- Pregnancy and neonatal outcomes, *eClinicalMedicine* 2023
- Circulating markers of microbial translocation, *eBioMedicine* 2023
- Molecular landscape, submitted

**Current focus**
- Emerging risk factors throughout the life course
- Novel biomarkers
- Preventive agents
- Microsimulation
Outline

- Evolving epidemiology of CRC
- Modifiable risk factors of early-onset CRC
  - Obesity
  - Metabolic dysregulation
  - Sedentary behavior
  - Diet
  - Microbial dysbiosis related exposures
Trends in adult overweight, obesity, and severe obesity
National Health Examination Survey/National Health and Nutrition Examination Surveys, 1960–2018

Recent birth cohorts of child/adolescent & younger adults:
1) Doubled obesity prevalence 2) Obese much earlier in life  3) Longer lifetime at risk
Obesity throughout life course vs. early-onset colorectal cancer

Critical time window?

Third Expert Report, World Cancer Research Fund, 2018

Liu et al., JAMA Oncology 2018
Levi et al., CEBP 2011
Kantor et al., Gut 2016
Li et al., Gastroenterology 2022

Early adulthood & weight change (√)

Midlife (√)

Birth weight (X?)

Childhood (?)

Maternal (?)

Murphy et al., Gut 2021

Stronger associations among recent birth cohorts?

How much obesity has contributed to the rising incidence of EO-CRC?
Bariatric surgery vs. CRC risk

Clapp et al., BJS 2023
Metabolic dysregulation vs. EO-CRC

Chen et al., Gut 2021

- 1 (ref)
- 1.09
- 1.12
- 1.31

No. of metabolic comorbid conditions

- hypertension, hyperlipidemia, hyperglycemia/type 2 diabetes, and obesity

Li et al., Gastro Hep Advances 2022

Type 2 diabetes

- Any: 1.24
- Controlled: 1.13
- Uncontrolled: 1.37
- Complicated: 1.59
Control of type 2 diabetes among adolescents and younger adults


<table>
<thead>
<tr>
<th>Variable</th>
<th>Use of Glucose-Lowering Medication in Persons with Glycated Hemoglobin Level of ≥7%</th>
<th>Use of Blood-Pressure-Lowering Medication in Persons with Blood Pressure of ≥140/90 mm Hg</th>
<th>Use of Statin Medication in Persons with Non-HDL Cholesterol Level of ≥130 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–44 yr</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>Statin (vs. No Statin)</td>
</tr>
<tr>
<td>45–64 yr</td>
<td>1.59 (1.00–2.55)</td>
<td>2.59 (1.62–4.14)</td>
<td>3.31 (1.50–7.34)</td>
</tr>
<tr>
<td>65 yr</td>
<td>1.85 (1.16–2.93)</td>
<td>2.21 (1.38–3.53)</td>
<td>5.60 (2.55–12.30)</td>
</tr>
</tbody>
</table>

Wang et al., JAMA 2021
Fang et al., NEJM 2021
Lascar et al., Lancet Diabetes Endocrinol 2018

Type 2 diabetes in adolescents and young adults

The prevalence of type 2 diabetes in adolescents and young adults is dramatically increasing. Similar to older-onset type 2 diabetes, the major predisposing risk factors are obesity, family history, and sedentary lifestyle. Onset of diabetes at a younger age (defined here as up to age 40 years) is associated with longer disease exposure and increased risk for chronic complications. Young-onset type 2 diabetes also affects more individuals of working age, accentuating the adverse societal effects of the disease. Furthermore, evidence is accumulating that young-onset type 2 diabetes has a more aggressive disease phenotype, leading to premature development of complications, with adverse effects on quality of life and unfavourable effects on long-term outcomes, raising the possibility of a future public health catastrophe. In this Review, we describe the epidemiology and existing knowledge regarding pathophysiology, risk factors, complications, and management of type 2 diabetes in adolescents and young adults.
Sitting watching TV/videos vs. EO-CRC by anatomic site

Prospective cohort, NHSII 1991-2011

Nguyen et al., JNCI Cancer Spectrum 2019

**Colon Cancer**

<table>
<thead>
<tr>
<th>Hours per week</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>8-14</td>
<td>0.90</td>
</tr>
<tr>
<td>&gt;14</td>
<td>1.47</td>
</tr>
</tbody>
</table>

P for trend = 0.22

**Rectal Cancer**

<table>
<thead>
<tr>
<th>Hours per week</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>8-14</td>
<td>1.91</td>
</tr>
<tr>
<td>&gt;14</td>
<td>2.44</td>
</tr>
</tbody>
</table>

P for trend = 0.04
Trends of sedentary behaviors (TV/video watching & computer use)
NHANES 2001-2016

Yang et al, JAMA, 2019
Measurement of diet quality:
A priori dietary patterns

<table>
<thead>
<tr>
<th>Dietary Component</th>
<th>DASH(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits</td>
<td>Quintiles (1pt=Q1, 5pt=Q5)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Quintiles (1pt=Q1, 5pt=Q5)</td>
</tr>
<tr>
<td>Whole grains</td>
<td>Quintiles (1pt=Q1, 5pt=Q5)</td>
</tr>
<tr>
<td>Nuts(^4)</td>
<td>Quintiles (1pt=Q1, 5pt=Q5)</td>
</tr>
<tr>
<td>Legumes(^4)</td>
<td>Quintiles (1pt=Q1, 5pt=Q5)</td>
</tr>
<tr>
<td>Low-fat dairy</td>
<td>Quintiles (1pt=Q1, 5pt=Q5)</td>
</tr>
<tr>
<td>Red/processed meat</td>
<td>Quintiles (1pt=Q5, 5pt=Q1)</td>
</tr>
<tr>
<td>Sugar-sweetened beverage(^5)</td>
<td>Quintiles (1pt=Q5, 5pt=Q1)</td>
</tr>
<tr>
<td>Sodium intake</td>
<td>Quintiles (1pt=Q5, 5pt=Q1)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>--</td>
</tr>
<tr>
<td>Fish</td>
<td>--</td>
</tr>
<tr>
<td>MUFA: SFA ratio</td>
<td>--</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>--</td>
</tr>
<tr>
<td>Omega-3 fatty acid</td>
<td>--</td>
</tr>
<tr>
<td>Trans fat</td>
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</tbody>
</table>

DASH, Dietary Approaches to Stop Hypertension; AMED, Alternative Mediterranean Diet; AHEI-2010, Alternative Healthy Eating Index-2010; MUFA, monounsaturated fat; SFA, saturated fat
Measurement of diet quality: A posteriori (data-driven) dietary patterns

- Principal component analyses: a method of dimension reduction that identifies underlying patterns in dietary intake data based on maximizing the variance between the different dietary factors.

- Number of components, weighting, and labelling of dietary patterns can vary greatly across studies.

Steck & Murphy, Nature Reviews Cancer 2020
Diet quality is poorer in the young & recent generations

The primary score is based on total fruits and vegetables, whole grains, fish and shellfish, sugar-sweetened beverages, and sodium.

Diet quality vs. early-onset colorectal adenoma
Prospective cohort, NHSII 1991-2011

Zheng* and Hur* et al, JNCI 2021
Deriving a sulfur microbial diet for CRC prevention

Nguyen et al. Gastroenterology. 2020
Sulfur microbial diet associated with early but not late-onset adenomas (age < 50 years)

**Early-onset adenoma**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Multivariable HR</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Ref)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1.05</td>
<td>1.05</td>
<td>0.02</td>
</tr>
<tr>
<td>1.03</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>1.31</td>
<td>1.31</td>
<td></td>
</tr>
</tbody>
</table>

**Late-onset adenoma**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Multivariable HR</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Ref)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1.05</td>
<td>1.05</td>
<td>0.68</td>
</tr>
<tr>
<td>0.93</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>0.99</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

P for trend = 0.02 for early-onset adenoma, P for trend = 0.68 for late-onset adenoma

Nguyen LH* & Cao Y*, et al. Gastroenterology. 2021
Umbrella review of meta-analyses of food/nutrient for 11 cancer sites

Papadimitriou et al, Nature Communications, 2021
Alcohol intakes peaks in early adulthood

Adolescence & early adulthood
- Lifetime peak in alcohol consumption
- High-risk drinking behaviors

Britton et al. *BMC Medicine* 2015
Alcohol intake in early adulthood vs. CRC later in life


P for trend = 0.02

Alcohol intake in early adulthood, g/day

Hur et al. Eur J Epidemiol 2021
Sugar-sweetened beverages intake the highest in aged <40

SSB intake throughout the life course vs. EO-CRC
NHSII 1991-2015

Mid-adulthood

RR (95% CI) per serving/d increase: 1.16 (1.00-1.36)
P for trend = 0.02

Adolescence

RR (95% CI) per serving/d increase: 1.32 (1.00-1.75)
P for trend = 0.01

Hur et al., Gut 2021
Replacement of SSBs with other beverages and risk of EO-CRC
NHSII 1991-2015

<table>
<thead>
<tr>
<th>Substitution</th>
<th>HR (95% CI) per serving/d increase</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificially sweetened beverages</td>
<td>0.83 (0.69-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fruit juice</td>
<td>1.02 (0.61-1.69)</td>
<td>0.95</td>
</tr>
<tr>
<td>Water</td>
<td>0.89 (0.74-1.07)</td>
<td>0.23</td>
</tr>
<tr>
<td>Tea</td>
<td>0.83 (0.65-1.06)</td>
<td>0.13</td>
</tr>
<tr>
<td>Coffee</td>
<td>0.82 (0.68-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Reduced fat milk</td>
<td>0.65 (0.47-0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total milk</td>
<td>0.64 (0.46-0.89)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Hur et al., Gut 2021
Antibiotics vs. adenoma/CRC/EO-CRC
Modest associations that likely vary by tumor location/antibiotic class
Swedish registers 2005-2016

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Antibiotics use</th>
<th>Proximal Colon</th>
<th>Distal Colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case (n) / Control (n)</td>
<td>Adjusted OR(^b) (95% CI)</td>
<td>Case (n) / Control (n)</td>
<td>Adjusted OR(^b) (95% CI)</td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
<td>No use</td>
<td>205 / 1 028</td>
<td>1 (Reference)</td>
<td>259 / 1 259</td>
</tr>
<tr>
<td>(early onset)</td>
<td>Low</td>
<td>58 / 327</td>
<td>0.87 (0.62-1.21)</td>
<td>70 / 368</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>219 / 1 039</td>
<td>0.99 (0.79-1.25)</td>
<td>236 / 1 203</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>37 / 245</td>
<td>0.60 (0.39-0.92)</td>
<td>47 / 254</td>
</tr>
<tr>
<td></td>
<td>Very high</td>
<td>16 / 36</td>
<td>1.53 (0.77-3.07)</td>
<td>12 / 36</td>
</tr>
<tr>
<td></td>
<td>P(_{trend}) (^c)</td>
<td>0.51</td>
<td>0.27</td>
<td>0.48</td>
</tr>
<tr>
<td>Age ≥ 50 years</td>
<td>No use</td>
<td>4 287 / 23 529</td>
<td>1 (Reference)</td>
<td>3 792 / 19 423</td>
</tr>
<tr>
<td>((n=38 095))</td>
<td>Low</td>
<td>1 649 / 8 311</td>
<td>1.08 (1.01-1.15)</td>
<td>1 315 / 6 534</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>5 999 / 29 152</td>
<td>1.10 (1.05-1.15)</td>
<td>4 689 / 22 610</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1 803 / 8 207</td>
<td>1.11 (1.04-1.19)</td>
<td>1 165 / 6 211</td>
</tr>
<tr>
<td></td>
<td>Very high</td>
<td>492 / 1 951</td>
<td>1.16 (1.04-1.30)</td>
<td>279 / 1 422</td>
</tr>
<tr>
<td></td>
<td>P(_{trend}) (^c)</td>
<td>&lt;.001</td>
<td>.70</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Low (1-10 days), moderate (11-60 days), high (61-180 days), and very high (>180 days) use

Cao et al., Gut 2017
Lu et al., JNCI 2021
Nguyen*, Cao* et al, CTG 2022
Later-onset (UK Clinical Practice Research Datalink): Zheng et al., Gut 2019
Cesarean delivery rates increased substantially globally

Betran et al, Plos one 2016

USA 32.8%
Sweden 16.2%
USA 22.7%
Sweden 10.4%
Birth via C section vs. EO-CRC
Population-based case-control, Sweden 1973-2017

Cao et al., JAMA Network Open 2023
Conclusions

• The decline of CRC is slowing down due to the rising incidence of early-onset CRC
• EO-CRC risk factors are multifactorial
  • Emerging data support the role of metabolic/behavioral/diet/microbial related exposures throughout the life course in EO-CRC
• Calling for a comprehensive understanding of behavioral & environmental factors throughout the life course for recent generations
• Challenges and opportunities
  • Research infrastructure development
  • Cross-disciplinary collaborations
  • Imperative need for implementation studies to improve CRC prevention
  • Patient advocacy and engagement
Acknowledgements

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GECCO Consortium
Ulrike Peters
Memorial Sloan Kettering Cancer Center
Ann Zauber
Erasmus Medical Cancer
Iris Lansdorp-Vogelaar

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