12:00-12:15p ET  Welcome and Introductions: Andrea Andi (Dwyer) and Dr. Jose Perea

12:15- 12:40p ET  Unraveling EAO CRC Disparities: Dr. Andreana Holowatyj

12:40-12:50p ET  Discussion with Jose: Addressing Questions

12:50-1:00p ET  Addressing Specific Questions Posed before Webinar

1:00-1:30p ET  Discussion

1:30-1:50p ET  Overview of research and papers, funding mechanisms: Jose and Andi

1:50-2:00p ET  Close out and next steps: Jose
Objectives

- Understand the context of health disparities among patients with early-onset CRC;
- Summarize current literature on differences in health outcomes across early-onset CRC patient population subgroups; and
- Broaden knowledge in early-onset CRC and current research.
Unraveling early-onset colorectal cancer disparities worldwide
‘Black Panther’ Star Chadwick Boseman Dies of Cancer at 43

The actor also played groundbreaking figures like James Brown, Jackie Robinson and Thurgood Marshall.

What to Know About Colon Cancer

The cancer that killed Chadwick Boseman is the second-leading cause of cancer deaths in the United States, and rates are rising among younger people.
Outline

Background—Early-onset CRC

Disparities in early-onset CRC patterns & outcomes: a global look
  • Race/ethnicity, sex and geography
  • USA, Nigeria, Spain & Indonesia

Future early-onset CRC disparities research directions
Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer among young patients worldwide.

**Approximately 181,935 new cases of early-onset CRC (6.1%) diagnosed annually.**
CRC incidence rates among young persons continue to rise annually since 1992

- Trend is paralleled across many countries, including: Denmark, Taiwan, Korea, New Zealand, Australia, the UK, and China.

CRCs behave more aggressively in young patients compared with late-onset (50+ yo) cases

- Adverse CRC histological features more common among young patients
- Patients with early-onset CRC more likely to present with or develop metastatic disease vs late-onset cases
- Younger & older age associated with poorer OS/PFS among mCRC
- Disproportionate burden of CRC recurrence among young patients

Early-onset sporadic CRC is a biologically different disease from late-onset (50+ yo) sporadic CRC

- Imbalanced redox status is a distinct hallmark of early-onset sporadic CRC
- Obesity is a major factor in oxidative stress
- 233 German patients (14.6% with early-onset CRC)

Addressing social determinants to advance cancer health equity

- Determinants of individual cancer risk and survival: biological/genetic, environmental, behaviors, health care, social

- Social, economic, and geographic disparities cut across multiple other population characteristics, such as:
  - Race/ethnicity, age, disability status, sexual orientation or gender identity, or other characteristics historically linked to discrimination or exclusion
Early-onset CRC is a global epidemic
Proportion of CRCs occurring before age 50 is higher among non-white races/ethnicities

- CRC incidence rates are highest in non-Hispanic blacks followed closely by Alaska Natives
- The proportion of individuals with early-onset CRC is nearly two-fold higher among non-white races/ethnicities

Individuals born c.1990 have 2-fold colon & 4-fold rectal cancer risk vs individuals born c.1950

- Five out of every six early-onset CRC patients do not carry a germline mutation associated with cancer predisposition.

Etiologies underlying this CRC epidemic, particularly sporadic CRC, among young individuals remain unexplained.

Proportion of Hispanic adolescents & young adults diagnosed with CRC increases with younger age


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>15–19 yr</th>
<th>20–24 yr</th>
<th>25–29 yr</th>
<th>30–34 yr</th>
<th>35–39 yr</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>250</td>
<td>706</td>
<td>1,539</td>
<td>2,795</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>26</td>
<td>43.3</td>
<td>130</td>
<td>52.0</td>
<td>370</td>
<td>52.4</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>11</td>
<td>18.3</td>
<td>32</td>
<td>12.8</td>
<td>79</td>
<td>11.2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17</td>
<td>28.3</td>
<td>67</td>
<td>26.8</td>
<td>173</td>
<td>24.5</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>5</td>
<td>8.3</td>
<td>18</td>
<td>7.2</td>
<td>74</td>
<td>10.5</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>1</td>
<td>1.7</td>
<td>3</td>
<td>1.2</td>
<td>10</td>
<td>1.4</td>
</tr>
</tbody>
</table>

- Hispanic patients accounted for 21% of cases age 35-39 years up to 28.3% of 15-19 year old cases.

CRC disparities among Latino subpopulations defined by country of origin

CRC incidence rates in US Latinos are generally higher than those reported for most Latin American countries

Proportion of early-onset CRC cases highest among Mexicans & Central/South Americans (20%) and lowest in Cubans (4%) vs NHWs (7%)


<table>
<thead>
<tr>
<th>Age at DX</th>
<th>All Latinos N = 36,133</th>
<th>Mexican N = 9678</th>
<th>Puerto Rican N = 295</th>
<th>Cuban N = 558</th>
<th>Central/South American N = 2636</th>
<th>Other/NOS Latinos N = 22966</th>
<th>NH white N = 174710</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>&lt;50</td>
<td>5,839</td>
<td>16</td>
<td>1,900</td>
<td>20</td>
<td>27</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>50-65</td>
<td>12,496</td>
<td>35</td>
<td>3,464</td>
<td>36</td>
<td>90</td>
<td>31</td>
<td>118</td>
</tr>
<tr>
<td>&gt;65</td>
<td>17,798</td>
<td>49</td>
<td>4,314</td>
<td>44</td>
<td>178</td>
<td>60</td>
<td>416</td>
</tr>
</tbody>
</table>
Conclusions

• Younger age at diagnosis is associated with a higher propensity for right-sided tumors
  • Tumor site-specific risk factor profiles
  • Avoid conflation of appendix & right-sided colon tumors

• Hispanics diagnosed with early-onset CRC at younger ages vs Whites
  • Differences in cancer determinants among Latinos?

• Need for studies within early-onset CRC population subgroups
Early-onset CRC survival is significantly worse among non-Hispanic blacks vs non-Hispanic whites.


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NHW No.</th>
<th>NHW %</th>
<th>NHB No.</th>
<th>NHB %</th>
<th>H No.</th>
<th>H %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>19,497</td>
<td>69.3</td>
<td>4,384</td>
<td>15.6</td>
<td>4,264</td>
<td>15.1</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>708</td>
<td>3.6</td>
<td>146</td>
<td>3.3</td>
<td>268</td>
<td>6.3</td>
</tr>
<tr>
<td>30-39</td>
<td>3,664</td>
<td>18.8</td>
<td>811</td>
<td>18.5</td>
<td>1,110</td>
<td>26.0</td>
</tr>
<tr>
<td>40-49</td>
<td>15,125</td>
<td>77.6</td>
<td>3,427</td>
<td>78.2</td>
<td>2,886</td>
<td>67.7</td>
</tr>
<tr>
<td>Mean (SD), years</td>
<td>43.0</td>
<td>(5.7)</td>
<td>42.9</td>
<td>(5.6)</td>
<td>41.4</td>
<td>(6.5)</td>
</tr>
</tbody>
</table>

• Blacks had a 35% and 51% higher hazard of death in colon and rectum/rectosigmoid junction cancers, respectively, vs Whites.

Early-onset CRC survival is significantly worse among blacks vs whites, even in early-stage disease.

Overall survival curves adjusted for age, poverty, sex, surgery, and radiation therapy.

Early-onset CRC survival is significantly worse among males compared with females

- Males had a 15% and 20% higher hazard of death in colon and rectum/rectosigmoid junction cancers, respectively, vs females.

Conclusions

- Survival after early-onset CRC diagnosis is significantly worse among NHB vs NHWs, even among patients with early-stage disease.
- Men experienced significantly poorer CRC survival vs women.
- Further study needed to determine whether differences in tumor biology and/or treatment are associated with disparities in outcomes.
Counties with high early-onset CRC mortality are concentrated in the Southern US

Hot spots: counties with high rates of early-onset CRC mortality among men and women, based on 3 geospatial methodologies.


Datasource: Colorectal Cancer Hot Spots from CDC Underlying Causes of Death, 1999 - 2017
Marked shifts in early-onset CRC mortality hot spots specifically among women

- Approximately 1 in every 16 contiguous U.S. counties are female early-onset CRC hot spots
- 47% of female hot spot counties were located in the Midwest/Northeast


Conclusions

• Geographic disparities in early-onset CRC mortality persist across the US

• Individual & community-level features accounted for distinct variance patterns in early-onset CRC survival by hot spot classification

• Understanding the impact of community health behaviors—particularly in regions with high early-onset CRC mortality rates—is critical for tailoring strategies to reduce early-onset CRC disparities
The burden of early-onset CRC among rural Nigerians

- No current organized CRC screening programs in Nigeria

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>379</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td></td>
</tr>
<tr>
<td>&lt;30 Years</td>
<td>103   27.2</td>
</tr>
<tr>
<td>30-39 Years</td>
<td>124   32.7</td>
</tr>
<tr>
<td>40-49 Years</td>
<td>152   40.1</td>
</tr>
<tr>
<td>Mean, Years (std)</td>
<td>34.8 (8.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>158   41.7</td>
</tr>
<tr>
<td>Male</td>
<td>221   58.3</td>
</tr>
<tr>
<td>Tumor Site</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>86    22.7</td>
</tr>
<tr>
<td>Rectosigmoid Junction/Rectum</td>
<td>290   76.5</td>
</tr>
<tr>
<td>Unspecified</td>
<td>3     0.8</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>352   92.9</td>
</tr>
<tr>
<td>Signet Ring Cell Carcinoma</td>
<td>7    1.8</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>7    1.8</td>
</tr>
<tr>
<td>Other**</td>
<td>13    3.4</td>
</tr>
</tbody>
</table>

**Other histological subtypes include, but are not limited to: carcinoid tumor, small cell carcinoma, neuroendocrine tumor, gastrointestinal stromal tumor (GIST), medullary carcinoma, and carcinoma, not otherwise specified.

Holowatyj et al. JCO Global Oncology. 2020.
Age patterns of early-onset CRC among Nigerian and African American individuals

70.3% vs 92.6% of US & Nigerian populations are age younger than 54 years

Holowatyj et al. JCO Global Oncology. 2020. CIA World Factbook.
Distinct patterns of early-onset CRC among Nigerian and African American individuals

<table>
<thead>
<tr>
<th>Observational Study Estimate</th>
<th>Nigerian vs African American Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Age at Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>0.87 (0.86-0.89)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
</tr>
<tr>
<td>Male</td>
<td>1.16 (0.91-1.48)</td>
</tr>
<tr>
<td><strong>Tumor Site</strong></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Ref</td>
</tr>
<tr>
<td>Rectosigmoid Junction/Rectum</td>
<td>8.14 (6.23-10.62)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Ref</td>
</tr>
<tr>
<td>Signet Ring Cell Carcinoma</td>
<td>0.51 (0.21-1.26)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>0.59 (0.25-1.40)</td>
</tr>
<tr>
<td>Other**</td>
<td>0.11 (0.06-0.19)</td>
</tr>
</tbody>
</table>

*Adjusted for patient age, sex, tumor site and histology, as appropriate.
**Other histological subtypes include, but are not limited to: carcinoid tumor, small cell carcinoma, neuroendocrine tumor, gastrointestinal stromal tumor (GIST), medullary carcinoma, and carcinoma, not otherwise specified.

OR, odds ratio; CI, confidence interval; Ref, referent.

Young Nigerian patients with CRC were eight-fold more likely to be diagnosed with rectal tumors compared with young AA individuals in the US.

Holowatyj et al. JCO Global Oncology. 2020.
Conclusions

• Nearly 2/3 of Nigerian population with CRC were diagnosed with early-onset disease vs 1 of every 8 African Americans in the US

• Potential left-sided CRC shift in sub-Saharan Africa
  • Young Nigerians more likely to present with rectal tumors vs young African Americans
  • Rectal tumors more likely to present with signs/symptoms vs colon tumors
  • Distinct CRC presentation may be due to limited resources, unique biology, and patient beliefs

• Need to implement organized CRC screening programs in Nigeria
Prognostic factors of microsatellite stable CRC in young Spanish patients

- Nearly half of patients with early-onset MSS CRC had a positive history of colorectal polyps
- 92% of young patients with a polyp history presented with 1+ polyps after CRC diagnosis

<table>
<thead>
<tr>
<th>Study Population</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>177 (100)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>95 (54)</td>
</tr>
<tr>
<td>Female</td>
<td>82 (46)</td>
</tr>
<tr>
<td><strong>Tumor Site</strong></td>
<td></td>
</tr>
<tr>
<td>Right-sided colon</td>
<td>43 (24)</td>
</tr>
<tr>
<td>Left-sided colon</td>
<td>61 (35)</td>
</tr>
<tr>
<td>Rectum/rectosigmoid junction</td>
<td>73 (41)</td>
</tr>
<tr>
<td><strong>History of Colorectal Polyps</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>84 (47)</td>
</tr>
<tr>
<td>Yes</td>
<td>93 (53)</td>
</tr>
<tr>
<td>Before CRC</td>
<td>20 (22)</td>
</tr>
<tr>
<td>Synchronous to CRC</td>
<td>38 (41)</td>
</tr>
<tr>
<td>After CRC</td>
<td>86 (92)</td>
</tr>
<tr>
<td>Mean number of polyps (SD)</td>
<td>2.14 (3.6)</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>19 (11)</td>
</tr>
<tr>
<td><strong>CRC-Related Death</strong></td>
<td>47 (27)</td>
</tr>
<tr>
<td><strong>Overall survival, months (±SD)</strong></td>
<td>80.6 (±49.6)</td>
</tr>
<tr>
<td><strong>Disease-free survival, months (±SD)</strong></td>
<td>72 (±42.8)</td>
</tr>
</tbody>
</table>
Prognostic factors of microsatellite stable CRC in young Spanish patients

- Patients who presented with polyps after early-onset MSS CRC diagnosis had significantly improved survival vs cases with no polyps.

- Polyps were associated with >80% reduced hazard of CRC-specific death in adjusted models.

Conclusions

- Importance of comprehensive colorectal polyp characterization among patients with early-onset CRC
  - Clinical and molecular features unique to young patients

- Unknown prevalence of polyps among early-onset CRC patients, especially across population subgroups
Unique patterns of early-onset CRC among multiethnic Indonesians

- One-third of all Indonesians with CRC are diagnosed with early-onset disease
  - 83.2% of Indonesia’s population is younger than age 54 years
- No current organized CRC screening programs in Indonesia
- 6.9% of adult population is obese

Unpublished data; CIA World Factbook.
Distinct patterns of early-onset CRC persist worldwide: do phenotypes differ?

<table>
<thead>
<tr>
<th>USA</th>
<th>Spain</th>
<th>Indonesia</th>
<th>Nigeria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/10</td>
<td>1/10</td>
<td>3/10</td>
<td>6/10</td>
</tr>
<tr>
<td>37.2%</td>
<td>40.5%</td>
<td>45.5%</td>
<td>76.5%</td>
</tr>
<tr>
<td>53.4%</td>
<td>53.2%</td>
<td>47.3%</td>
<td>58.3%</td>
</tr>
</tbody>
</table>
Future early-onset CRC research directions

• Additional multi-omic studies of early-onset sporadic CRC across and within diverse population subgroups

• Multilevel research on dynamic relationships between individual factors, macroenvironmental influences, & health disparities in early-onset CRC

• Laboratory-based studies of early-onset CRC disparities

• Understanding survivorship needs among young CRC patients by population subgroups

• Large-scale international investigation of early-onset CRC to decipher potential phenotypic differences in disease burden worldwide
The overarching goal of GEOCODE is to decipher geographic variations in phenotypes of early-onset CRC worldwide.
Acknowledgements

Holowatyj Lab/Team
Dr. Jose Perea, MD, PhD
Mr. Faruk Mohammed, MS
Dr. Bens Pardamean, PhD
Dr. James Baurley, PhD
Dr. Justin Moore, PhD, MPH
Dr. Elena Stoffel, MD, MPH
Dr. Mark Lewis, MD
Dr. Cathy Eng, MD
Dr. Kay M. Washington, MD, PhD
Dr. Xingyi Guo, PhD
Ms. Andrea Dwyer
Ms. Reese Garcia

Funding Sources

Susan G. Komen Graduate Training in Disparities Research
National Institutes of Health/NHGRI (T32 HG008962)
Vanderbilt University Medical Center
Questions & Discussion

Andreana N. Holowatyj, PhD, MS
Andreana.Holowatyj@vumc.org
Twitter: @drholowatyj
Discussion
Discussion. Increasing incidence.
Discussion. CRC-related deaths in Spain.

Figure 2. Colorectal cancer mortality in Spain between 2010 and 2014 (classified by age intervals: 0-54, 55-74 and ≥75, respectively). Municipal distributions of the relative risks of death (A, B and C) and probabilities of having a relative risk greater than 1 (D, E, and F).
Discussion. CRC-related deaths in Spain.
Discussion. CRC-related deaths in Spain.
Discussion. CRC-related deaths in Spain.
Worldwide Consortium on EAOCRC characterization: GEOCODE.
Addressing Pre-Webinar Questions
Discussion
Research literature.

Open

Personal History of Diabetes as Important as Family History of Colorectal Cancer for Risk of Colorectal Cancer: A Nationwide Cohort Study

Uzair Ali Khan, MSc\textsuperscript{1,2}, Mahdi Fallah, MD, PhD\textsuperscript{1,2}, Yu Tian, PhD\textsuperscript{1,2}, Kristina Sundquist, MD, PhD\textsuperscript{3,4,5}, Jan Sundquist, MD, PhD\textsuperscript{3,4,5}, Hermann Brenner, MD, PhD\textsuperscript{1,5,7} and Elham Kharazmi, MD, PhD\textsuperscript{1,3}

Research literature.

AIM: Analysis of the association of CRC risk, especially early-onset CRC, with DM, family history of CRC, and age at DM diagnosis.

MATERIAL AND METHODS:

- Nationwide cohort study (Swedish family cancer data sets)

- All individuals born after 1931 and their parents (12,614,256 individuals; 559,375 diabetic patients; 162,226 CRC patients).


-
Research literature.

RESULTS:

DM diagnosis before 50: 1.9-fold increased risk of CRC before 50 vs 1.3-fold risk of CRC at/after the age of 50 years.

DM diagnosis before 50 in those with a family history of CRC was associated with 6.9-fold risk of CRC before 50, and 1.9-fold risk of CRC at/after the age of 50 years.

Diabetic patients had a similar lifetime risk of CRC before 50 (0.4%) to those with only a family history of CRC (0.5%), double that of the population (0.2%, 0.2%–0.2%).

**Research literature.**

**CONCLUSIONS:**

- DM is associated with increased risk of CRC in a magnitude close to having family history of CRC.

- Associations of DM and CRC family history with increased CRC risk were most prominent in young adults.

- These findings warrant further studies on CRC screening in patients with diabetes, especially type 2, at earlier ages than in the general population.

*Am J Gastroenterol 2020;115:1103–1109.*
Current Overview of EAOCRC initiatives.

Research literature.


Ngozi Enwerem, Moo Y. Cho, Joshua Demb, Ashley Earles, Karen M. Heskett, Lin Liu, Siddharth Singh, Samir Gupta

Clin Gastroenterol Hepatol 2020 May 16;S1542-3565(20)30679-0
AIM: Systematic review of young-onset adenoma (YOA) prevalence, associated risk factors, and rate of metachronous advanced neoplasia after YOA diagnosis.

RESULTS:
- The pooled overall prevalence of YOA was 9.0% (95% CI, 7.1%-11.4%) based on 24 studies comprising 23,142 individuals.
- Only advancing age was identified as a consistent risk factor for YOA (4 studies, 78,880 individuals).
- Pooled rate of metachronous advanced neoplasia after baseline YOA diagnosis was 6.0% (95% CI, 4.1%-8.6%) (3 studies, 1493) undergoing follow-up colonoscopy, with only 1 CRC case reported.
- Few studies reported metachronous advanced neoplasia and none evaluated whether routine surveillance colonoscopy decreases risk of CRC.
Research literature.

CONCLUSION:

More research is needed to understand the prevalence, risk factors, and risk of CRC associated with YOA.

Clin Gastroenterol Hepatol 2020 May 16;S1542-3565(20)30679-0
EAO CRC Funding Opportunities
- **Next webinar:**

  November, 3rd, 2020 (Tuesday, 12pm ET).

- **3rd EOCRC International Symposium.**

  Definitive days / Abstract submission.
LET´S KEEP UP THE EFFORTS.