Concurrent Session 2: Early Age Onset Colorectal Cancer Screening Updates

November 16, 2020
3:15 to 4:15 p.m. EST
PANELISTS

• Heather Hampel, MS, LGC, Associate Director, The Ohio State University Comprehensive Cancer Center, Human Genetics, NCCRT Steering Committee (Moderator)

• Rebecca L. Siegel, MPH, Scientific Director, Surveillance Research, American Cancer Society, Inc.

• Samir Gupta, MD, MSCS, AGAF, Professor, Division of Gastroenterology, Department of Internal Medicine; Co-Lead, Cancer Control Program, Moores Cancer Center; University of California San Diego; Chief, GI Section, San Diego Veterans Affairs Healthcare System

• Jordan J. Karlitz, MD, Director, GI Hereditary Cancer and Genetics Program, Tulane University Cancer Center; NCCRT Steering Committee
The epidemiology of early-onset colorectal cancer: Opportunities for Action

Rebecca Siegel, MPH
Sr Scientific Director of Surveillance Research
American Cancer Society
NCCRT Annual Meeting
November 16, 2020
### October 2020

<table>
<thead>
<tr>
<th>Population</th>
<th>Draft Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults ages 50 to 75 years</td>
<td>The USPSTF recommends screening for colorectal cancer in all adults ages 50 to 75 years. See the “Practice Considerations” section and Table 1 for details about screening strategies.</td>
<td>A</td>
</tr>
<tr>
<td>Adults ages 45 to 49 years</td>
<td><strong>The USPSTF recommends screening for colorectal cancer in adults ages 45 to 49 years.</strong></td>
<td>B</td>
</tr>
<tr>
<td>Adults ages 76 to 85 years</td>
<td>The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults ages 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient’s overall health and prior screening history.</td>
<td>C</td>
</tr>
</tbody>
</table>

---

### September 2018

The ACS recommends that adults aged 45 y and older with an average risk\(^b\) of CRC undergo regular screening, with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on noncolonoscopy screening tests should be followed up with timely colonoscopy.

The recommendation to begin screening at age 45 y is a **qualified recommendation**.

The recommendation for regular screening in adults aged 50 y and older is a **strong recommendation**.

The ACS recommends that average-risk adults in good health with a life expectancy of greater than 10 y continue CRC screening through the age of 75 y (**qualified recommendation**).

The ACS recommends that clinicians individualize CRC screening decisions for individuals aged 76 through 85 y based on patient preferences, life expectancy, health status, and prior screening history (**qualified recommendation**).

The ACS recommends that clinicians discourage individuals over age 85 y from continuing CRC screening (**qualified recommendation**).
CRC incidence & mortality in the U.S.
CRC incidence trends <65 y

0-49 yr

Rate per 100,000 population

Male
Female

44%

50-64 yr

Rate per 100,000 population

Male
Female

APC, -2.9
APC, +1.0

APC = annual percent change

Siegel et al. March 2020, CA A Cancer Journal for Clinicians
CRC mortality trends <50 y

#1 cancer COD in men <50 y

36% localized stage in women vs 31% in men

APC = annual percent change

Siegel et al. March 2020, CA A Cancer Journal for Clinicians
CRC mortality trends <65 y

#1 cancer COD in men <50 y

36% localized stage in women vs 31% in men

50-64 yr

APC = annual percent change

Siegel et al. March 2020, CA A Cancer Journal for Clinicians
CRC incidence age <50 yr by stage at diagnosis

APC = annual percent change

APC, +2.5

APC, -0.8 (nonsignificant)

APC, +2.5
CRC stage at diagnosis by age

Risk of advanced stage <50 40% higher after accounting for screening

Chen et al. 2017, Clin Gastro and Hep

Stage at diagnosis

LOCALIZED
- 0-49 years: 31%
- 50+ years: 37%

REGIONAL
- 0-49 years: 38%
- 50+ years: 35%

DISTANT
- 0-49 years: 26%
- 50+ years: 20%

UNKNOWN
- 0-49 years: 5%
- 50+ years: 8%

Data Source: NAACCR 2019, cases diagnosed 2012-2016.
CRC 5-year relative survival by age

Data Source: SEER 18, diagnoses during 2009-2015, all followed through 2016.
Median age at CRC diagnosis, 1990-2016

- 1990-91: 72 yrs
- 1995-96: 72 yrs
- 2000-01: 72 yrs
- 2005-06: 72 yrs
- 2010-11: 66 yrs
- 2015-16: 66 yrs

Siegel et al. March 2020, CA A Cancer Journal for Clinicians
CRC <50 y in the US 2020

- 17,930 new cases
  =49 per day

- 3,640 deaths
  =10 per day

80% have children <18 y

Source: Siegel et al. March 2020, CA A Cancer Journal for Clinicians
CRC subsite distribution by age

<50 y

- Proximal: 4%
- Distal: 23%
- Rectal: 37%
- Appendix: 10%
- Large Intestine, NOS: 25%

65+ y

- Proximal: 23%
- Distal: 49%
- Rectal: 19%
- Appendix: 2%
- Large Intestine, NOS: 7%
**CRC subsite distribution by age**

**<50 y**
- Proximal: 10%
- Distal: 25%
- Rectal: 37%
- Appendix: 23%
- Large Intestine, NOS: 4%

**65+ y**
- Proximal: 49%
- Distal: 19%
- Rectal: 23%
- Appendix: 7%
- Large Intestine, NOS: 2%
CRC age distribution <50 yr

- 45-49 years: 44%
- 30-39 years: 22%
- 40-44 years: 24%
- 0-29 years: 10%
“unique molecular and clinicopathologic features in patients younger than 30 years and with predisposing conditions.”

Substantial opportunity to mitigate burden:

- Screen average-risk at 45 – go FIT!
- Earlier for high risk (fam history)
- Reducing delays in diagnosis/tx
  - Educate
  - Reduce stigma
Thank you!
A Different Perspective on the Utilization of SEER Cancer Data to Understand EAOCRC

JORDAN J. KARLITZ, MD
ASSOCIATE PROFESSOR OF MEDICINE, DIVISION OF GASTROENTEROLOGY
TULANE UNIVERSITY SCHOOL OF MEDICINE
Analyzing SEER Cancer Data in One-year Age Increments

- Traditionally, SEER data has been analyzed in age group blocks (age 30-39, 40-49 etc.)
- Pooling of ages can increase statistical power for analyses
- However, can potentially overlook important trends in cancer incidence
- Large size of SEER database allows analyses in one-year age intervals
  - Allows for “high definition” view of incidence rate trends in those approaching screening age (key group given rising IRs in young patients)
SEER (Surveillance, Epidemiology, and End Results Program) Database: Overview

- **SEER 9** - Available for cases diagnosed from 1975 through the current data year.
- **SEER 13** - Available for cases diagnosed from 1992 through the current data year and includes expanded races.
- **SEER 18** - Available for cases diagnosed from 2000 through the current data year and includes expanded races.
- **SEER 21** - Available for cases diagnosed from 2000 through the current data year and includes expanded races. SEER21 has a more limited set of available variables than other groupings and is only available for limited statistics.
- Detroit and New Jersey are no longer in the SEER Program, but are included in the current data release.
- Ref: https://seer.cancer.gov/registries/terms.html

*Subcontract under New Mexico
**Three regions represent the state of California: Greater Bay, Los Angeles, and Greater California
***Research support registry only; not under contract to submit data

Georgia includes Atlanta, Rural Georgia and Greater Georgia
Trends in the incidence of colorectal cancer in the U.S. among those approaching screening age

- Unique methodology: analyze SEER 18 CRC incidence rates in one year age increments

- **Question**: What is the increase in the CRC incidence rate from 49 to 50 years of age, when large segments of the population begin average-risk screening?

- 170,434 cases of CRC were analyzed

- Incidence rate increase of **46.1%** from 49 to 50 years of age

- Findings consistent with preexisting CRCs diagnosed via screening uptake

- Supports the presence of a large undetected preclinical case burden in patients younger than 50 years that is not reflected in observed SEER incidence rates
**Findings** support large undetected pre-clinical CRC burden prior to age 50 (not reflected in SEER IRs) ultimately diagnosed with screening at age 50.

**Argues for screening at age 45**

Colorectal Cancer Incidence Rates per 100,000 Population in 1-Year Age Increments in the US Surveillance, Epidemiology, and End Results 18 Registries Among Patients Aged 30 to 60 Years, 2000-2015. Only adenocarcinomas were analyzed. The arrowhead indicates the incidence rate increase from 49 to 50 years of age (46.1% increase: 34.9 [95% CI, 34.1-35.8] to 51.0 [95% CI, 50.0-52.1] per 100,000 population).


Case counts: there were approximately 129,226 CRCs (*extrapolated to all 50 states) from patients aged 45 to 50 years from 2000 to 2015.
Age 49 to 50 Incidence Rate Increase Reproducible Across Different Patient Groups

- All U.S. Regions
- Men and Women
- Whites and Blacks
- Colon and Rectal Cancers

Screening at age 50 unifies these disparate populations, supporting that this increase in incidence from 49 to 50 is due to screening detection as opposed to advancing age alone.
Figure 1. 2000-2015 Colorectal Cancer Incidence Rates per 100,000 in One Year Age Increments for United States Regions (West, South, Northeast, Midwest) Age 30-60

South: 35.5%
Northeast: 56.0%
Midwest: 53.7%
West: 47.8%

Blue Arrows: Pointing to Age 49 to 50 Incidence Rate Inflation in all 4 Regions
Colored Boxes Indicate Percentage Increase from Age 49 to 50 in Each Region
Men and Women

Males: 52.9%
Females: 39.1%
Race Stratification

Blacks: 47.3%
Whites: 46.2%
Colon and Rectal Cancer

Rectal cancer % increase lower than colon cancer because rectal more likely to present with symptoms prior to screening detection
Key Points
- 92.9% of CRC diagnosed at age 50 are invasive (beyond in situ stage)
- Localized cancers: 10% to 11% 5-year mortality, and most require surgery (argues against length time bias in which slower growing and potentially less clinically significant tumors are detected with screening)
- Localized and regional CRCs may be associated with psychological distress, economic burden, and impaired quality of life
- Expected distant CRCs would not have steep rate increases from 49 to 50 years of age as more likely to present with symptoms prior to screening
Take Home Points From This Study

- Steep age 49 to 50 incidence rate increase supports presence of large pre-clinical cancer burden in those in their 40’s not reflected in observed SEER incidence rates.

- Arguments historically posed against earlier screening at age 45 include much lower incidence rates in 45-49 (34/100,000) versus 50-54 (60.2/100,000).
  - Misconception as those 45-49 do not have the advantage of having CRCs picked up by screening (mainly only by symptoms or FH) compared to 50-54 year-olds.
  - Comparing apples to oranges.
Prevalence of colorectal neoplasia by age in an average risk cohort: Further Evidence that risk in 45-49-year-olds is similar to 50-54-year-olds

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt; 40 (n=2451)</th>
<th>40-44 (n=1288)</th>
<th>45-49 (n=1870)</th>
<th>50-54 (n=2216)</th>
<th>55-59 (n=6936)</th>
<th>60+ (n=7895)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced neoplasia</td>
<td>1.1% (n=28)</td>
<td>3.0% (n=38)</td>
<td><strong>3.7%</strong> (n=70)</td>
<td>3.6% (n=804)</td>
<td>5.1% (n=355)</td>
<td><strong>6.9%</strong> (n=541)</td>
</tr>
<tr>
<td>Clinically significant serrated polyp</td>
<td>3.0% (n=73)</td>
<td>5.1% (n=66)</td>
<td><strong>5.9%</strong> (n=110)</td>
<td><strong>6.1%</strong> (1350)</td>
<td>6.6% (n=455)</td>
<td>6.0% (n=471)</td>
</tr>
</tbody>
</table>

Utilized the New Hampshire Colonoscopy Registry to compare the prevalence of advanced neoplasia (AN) in an "average-risk screening equivalent" group aged 45-49 years with patients aged 50-54 years and older receiving screening colonoscopy.

NCCRT 2020: Early Onset CRC Screening Updates
Current opportunities based on family history and symptoms

Samir Gupta MD, MSCS
Professor, Department of Medicine, UC San Diego
Chief, GI Section, VA San Diego
s1gupta@health.ucsd.edu
@samirguptaGl
Family history increases risk and “left shifts” age of diagnosis

<table>
<thead>
<tr>
<th>≥ 1 first degree relative with CRC at age:</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 y</td>
<td>3.31 (2.79–3.89)</td>
</tr>
<tr>
<td>&gt;50 y</td>
<td>2.02 (1.93–2.11)</td>
</tr>
<tr>
<td>&gt;60 y</td>
<td>1.99 (1.90–2.09)</td>
</tr>
</tbody>
</table>
Family history-based recommendations well established

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Guideline by American Cancer Society, US Multi-Society Task Force on Colorectal Cancer (USMSTF®) and American College of Radiology, 2008&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>CRC or advanced adenoma in 2 first degree relatives at any age OR CRC or adenoma in a single first degree relative &lt; age 60 years</td>
<td>Colonoscopy every 5 years beginning 10 years prior to age of first degree relative diagnosis or age 40</td>
</tr>
<tr>
<td>CRC or adenoma in single first degree relative diagnosed age &gt;=60 OR CRC in 2 second degree relatives at any age</td>
<td>Begin screening at age 40 with any test</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network 2019</td>
<td></td>
</tr>
<tr>
<td>CRC &gt;=1 first degree relative with CRC at any age</td>
<td>Colonoscopy at age 40 or 10 years before earliest diagnosis of CRC, repeat every 5 years</td>
</tr>
</tbody>
</table>
Potential effectiveness of implementation of family history based guidelines unclear

• Aims:
  • Estimate performance of family-history based guidelines for identifying individuals with early onset CRC

• Methods:
  • Population-based case control study individuals age 40-49 in the Colon Cancer Family Registry 1998-2007
  • Compared sensitivity and specificity of guidelines from major groups
  • Estimated proportion with CRC who could have been recommended screening initiation younger than age of diagnosis
Figure 1. Potential impact of family history-based guidelines on time of colorectal cancer (CRC) diagnosis. Of 2473 cases of CRC, approximately 25% met the criteria for early screening. Among 614 CRC cases meeting the criteria for early screening, approximately 98% could have been recommended to initiate screening at an age younger than the actual age at the time of diagnosis of CRC.
Current opportunities: on-time evaluation of symptoms

- Small single center case control study, younger vs older rectal cancer patients had longer median time from
  - Symptom onset to healthcare provider evaluation: 121 vs 21 days
  - Symptom onset to first course of treatment: 217 vs 58 days
- Single center retrospective study, younger vs older CRC patients had longer time from
  - Symptom onset to diagnosis: median 128 vs 79 days, with average 243 vs 154 days
  - First medical visit to diagnosis: median 31 vs 22 days, with average of 91 vs 67 days

Strategy for timely evaluation of signs and symptoms

**ID Red Flags**
- Rectal bleeding
- Abdominal Pain
- Weight Loss
- Iron Deficiency Anemia
- Constipation
- Diarrhea

**Triage**
To immediate colonoscopy vs other work up or treatment using:
- Clinical Guidelines
- Symptom/Sign Severity
- Clinical context

**Close the Loop**
Example Strategy:
- Mandatory 30 day clinic follow up to ensure resolution

Burnett-Hartman AN; Lee JK; Demb J; Gupta S under review; Figure concept courtesy of Josh Demb, PhD; Credit to Jeff Lee, MD for “clinical loop”
Thank You!

• Acknowledgements
  • Grant Support:
    • NCI 1UG3CA233314-01A1
    • NCI Cancer Center Support Grant CA023100-32
  • Colon Cancer Family Registry
• Contact:
  • s1gupta@health.ucsd.edu
  • @samirguptaGI
# Family history-based recommendations

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC or advanced adenoma in 2 first degree relatives at any age OR CRC or adenoma in a single first degree relative &lt; age 60 years</td>
<td>Colonoscopy every 5 years beginning 10 years prior to age of first degree relative diagnosis or age 40</td>
</tr>
<tr>
<td>CRC or adenoma in single first degree relative diagnosed age &gt;=60 OR CRC in 2 second degree relatives at any age</td>
<td>Begin screening at age 40 with any test</td>
</tr>
<tr>
<td>CRC or advanced adenoma in 2 first degree relatives at any age OR CRC or advanced adenoma in a single first degree relative &lt; age 60 years</td>
<td>Colonoscopy every 5 years beginning 10 years prior to age of first degree relative diagnosis or age 40</td>
</tr>
<tr>
<td>CRC or advanced adenoma in single first degree relative diagnosed age &gt;=60</td>
<td>Begin screening at age 40 with any test</td>
</tr>
<tr>
<td>CRC &gt;=1 first degree relative with CRC at any age</td>
<td>Colonoscopy at age 40 or 10 years before earliest diagnosis of CRC, repeat every 5 years</td>
</tr>
<tr>
<td>CRC in 2 or more first degree relatives</td>
<td>Colonoscopy every 5 years at age 40 or 10 years younger than age of diagnosis of earliest diagnosed first degree relative, whichever is earlier</td>
</tr>
<tr>
<td>CRC in 1 first degree relative</td>
<td>Colonoscopy every 5-10 years at age 40-50 years or 10 years younger than age of diagnosis of first degree relative, whichever is earlier. FIT every 1-2 years is suggested as 2nd line option</td>
</tr>
<tr>
<td>1 or more first degree relative with documented advanced adenoma</td>
<td>No recommendation for a preferred test. Colonoscopy or FIT are both options. Colonoscopy every 5-10 years at age 40-50 years or 10 years younger than age of diagnosis of first degree relative, whichever is earlier. FIT every 1-2 years is suggested as 2nd line option</td>
</tr>
</tbody>
</table>
Despite recommendations, proportion up-to-date probably low

- Aim: estimate colonoscopy exposure using US National Health Interview Survey data from 2005 and 2010
- Age 40 and older
- Survey included questions about whether a mother/father/sibling, or child had cancer, and type of cancer
Results

Key Finding
38.3% individuals age 40-49 reporting first degree relative with CRC were up to date with colonoscopy in 2010

Limitations and Strengths:
- No data below age 40
- Data from 2010
- Population-based estimate
### TABLE 3. Sensitivity and Specificity of Family History-Based Criteria Issued by the ACS, NCCN, USMSTF, and CAN for Identifying Patients Aged 40 to 49 Years With Early-Onset CRC

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS 2008&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25%</td>
<td>90%</td>
</tr>
<tr>
<td>NCCN 2017</td>
<td>21%</td>
<td>92%</td>
</tr>
<tr>
<td>USMSTF 2017</td>
<td>21%</td>
<td>92%</td>
</tr>
<tr>
<td>CAN 2018</td>
<td>21%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, American Cancer Society; CAN; Joint Canada/American Gastroenterological Association; CRC, colorectal cancer; NCCN, National Comprehensive Cancer Network; USMSTF, US Multi-Society Task Force on Colorectal Cancer.

<sup>a</sup> Joint recommendations by the ACS, USMSTF, and American College of Radiology in 2008.
Population Screening for Common Inherited Diseases

- **CDC Tier 1 Diseases:** Lynch syndrome, Hereditary Breast-Ovarian Cancer syndrome, & Familial Hypercholesterolemia
  - Common
  - Easy, Accurate Testing Available
  - Actionable

- Several ongoing projects offering genetic testing for these diseases to the general public
- Geisinger MyCode assessed for Tier 1 conditions in 50,000 participants
- 1.32% (1 in 76 individuals) had one of these conditions
- Compare to the 1 in 800 positive rate in newborn screening programs

Murray, M. [https://www.ncbi.nlm.nih.gov/books/NBK500389/]
Population Screening for Common Inherited Diseases

- Healthy Nevada Project: March 2018 phase two expanded to an additional 40,000 participants with genetic testing partner Helix
- Notifying study volunteers at risk for CDC Tier 1 conditions: Hereditary Breast Ovarian Cancer, Lynch syndrome, and Familial Hypercholesterolemia
- 299 (1.26%) of 23,713 participants have a P/LP variant in the 9 genes responsible for these conditions (1 in 79 individuals)
  - >90% of carriers were undetected under current medical practice
  - <20% had documented suspicion for inherited genetic disease in EMR
  - <40% had family history of relevant disease
- A population preventative genetic screening approach for people <45 may improve outcomes

Grzymski, JJ. https://www.biorxiv.org/content/10.1101/650549v1
Points for Discussion

- Incidence of EOCRC is increasing, particularly rectal cancer and cause is not known (Siegel)

- Steep jump in incidence of CRC from age 49 to 50 indicates that these cancers begin prior to age 50 but are not detected until general population screening begins at age 50 – will start age of 45 help? (Karlitz)

- 25% of CRC patients have a FDR with CRC and could have been recommended to start screening early; 98% would have started screening prior to their age at diagnosis (Gupta)

- Should population screening be considered to identify individuals with hereditary cancer syndromes who need to start colonoscopy the earliest and repeat it every 1-2 years (Hampel)

- For those without family history, early symptom identification & prompt follow-up is our best option (Gupta)
A CANCER-FREE WORLD BEGINS HERE
Concurrent Session 2: Early Age Onset Colorectal Cancer Screening Updates

November 16, 2020
3:15 to 4:15 p.m. EST