Natural History and Epidemiology of Colorectal Cancer

Prevent Cancer Foundation
2018 Dialogue for Action
April 11, 2018

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Disclaimers

• I am a member of the Advisory Board of the Mississippi Cancer Registry and the Medical/Research Advisor to the Mississippi Partnership for Comprehensive Cancer Control Executive Board; these are uncompensated voluntary appointments.

• Otherwise, I have no conflicts of interest to disclose.

• The statements and views expressed in this presentation are my own and may not reflect the opinions of the University of Mississippi Medical Center or any other organization with which I am associated.
Why focus on colorectal cancer?

• CRC is highly preventable & declining in most states.

• CRC is 2\textsuperscript{nd} 3\textsuperscript{rd} most common cancer in men + women.
  ➢ Estimated 97,220 new cases of colon cancer in 2018 (source: ACS)
  ➢ Estimated 43,030 new cases of rectal cancer in 2018 (source: ACS)

• CRC is 2\textsuperscript{nd} leading cause of cancer death in men + women.
  • Estimated 50,630 deaths during 2018 (source: ACS)

• CRC treatment costs are 2\textsuperscript{nd} highest of all cancer sites.

• CRC screens are net cost-\textbf{SAVING}.
### Learning objectives of this presentation

<table>
<thead>
<tr>
<th>Topic to be covered</th>
<th>Take-home message</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence of development from polyp to cancer</td>
<td>CRC cancer biology explains why prevention is highly effective, but atypical CRC cancer biology may shed light on future progress</td>
</tr>
<tr>
<td>Screening options</td>
<td>Many choices available for preventive and early-detection screens, which all require colonoscopy for diagnostic confirmation</td>
</tr>
<tr>
<td>CRC screening effectiveness requires effective therapy</td>
<td>Early identification of CRC via screening results in optimal outcomes with less toxic, less expensive medical procedures</td>
</tr>
<tr>
<td>Epidemiology of colorectal cancer</td>
<td>Dynamic changes in CRC epidemiology reflect changing landscape of disparately-distributed positive &amp; negative risk factors</td>
</tr>
<tr>
<td>Increased incidence of colorectal cancer in people younger than 50</td>
<td>Causes of recent trends are unknown; requires physicians' attention to symptoms to avoid delays in diagnosis &amp; treatment</td>
</tr>
<tr>
<td>Genetics and colorectal cancer</td>
<td>Genetic factors can identify young high-risk individuals and may be useful in treatment decisions</td>
</tr>
<tr>
<td>Risk factors associated with colorectal cancer</td>
<td>CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.</td>
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</table>
A generalized (Vogelstein) model of CRC development & progression

- Adenoma is precursor to CRC, rarely occurs in individuals under 49, adenomas & CRC more prevalent later in life.
- In the 6th, 7th, and 8th decades of life the prevalence of adenomas increases.
- The dwell time of an early to advanced adenoma ~2-5 years.
- Similarly, the dwell time of an advanced adenoma to early cancer ~2-5 years.
Flexible fiber optics revolutionized CRC prevention & control in 1973 with the introduction of colonoscopy

“Polypectomy Via the Fiberoptic Colonoscope — Removal of Neoplasms beyond Reach of the Sigmoidoscope”
published in the *New England Journal of Medicine*
(288:329-332)
on February 15, 1973
by
William I. Wolff, M.D. and Hiromi Shinya, M.D.
Can colonoscopy / polypectomy *alone* eliminate CRC mortality?

- <10% of all adenomas become cancerous, but
- > 95% of colorectal cancers develop from adenomas.


Do atypical CRCs with early metastatic tendencies adversely affect survival outcomes? Does this signal a need for changing clinical practice guidelines?

Why does screening matter?
Because survival is tremendously improved by early-stage diagnosis
(SEER 2005-2011 Data, All Races, Both Sexes)

Percent of Cases by Stage

- **Distant (20%)**
  - Cancer Has Metastasized
- **Localized (39%)**
  - Confined to Primary Site
- **Regional (36%)**
  - Spread to Regional Lymph Nodes
- **Unknown (5%)**
  - Unstaged

5-Year Relative Survival

- **Localized**
  - 90.1%
- **Regional**
  - 70.8%
- **Distant**
  - 13.1%
- **Unstaged**
  - 34.5%
<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Description</th>
<th>United States Preventive Services Task Force (USPSTF)</th>
<th>American Cancer Society–U.S. Multi-Society Task Force (ACS-USMSTF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal occult blood test (FOBT)* and fecal immunochemical test (FIT)*</td>
<td>Examination of the stool for traces of blood not visible to the naked eye</td>
<td>Recommends high-sensitivity FOBT and FIT annually for ages 50-75</td>
<td>Recommends high-sensitivity FOBT and FIT annually for ages ≥ 50</td>
</tr>
<tr>
<td>Sigmoidoscopy*</td>
<td>Internal examination of the lower part of the large intestine</td>
<td>Recommends every 5 years with high-sensitivity FOBT every 3 years for ages 50-75</td>
<td>Age ≥ 50, every 5 years</td>
</tr>
<tr>
<td>Double-contrast barium enema*</td>
<td>X-ray examination of the colon</td>
<td>--</td>
<td>Age ≥ 50, every 5 years</td>
</tr>
<tr>
<td>Colonoscopy* *Positive findings require follow-up colonoscopy</td>
<td>Internal examination of the entire large intestine</td>
<td>Recommends every 10 years for ages 50-75</td>
<td>Age ≥ 50, every 10 years</td>
</tr>
<tr>
<td>Computed tomography colonography*</td>
<td>Examination of the colon and rectum using pictures obtained using a computed tomography scanner</td>
<td>Age ≥ 50, every 5 years</td>
<td>Age ≥ 50, every 5 years</td>
</tr>
<tr>
<td>Fecal DNA*</td>
<td>Examination of the stool for traces of colorectal cancer DNA</td>
<td>Age ≥ 50, every 1 or 3 years</td>
<td>Age ≥ 50, every 3 years</td>
</tr>
</tbody>
</table>
Implementing colonoscopy navigation improves practice-centered outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention Group N = 131</th>
<th>Control Group N = 75</th>
<th>Intervention Group Versus Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy completed (w/in 12 m)</td>
<td>96.2%</td>
<td>69.3%</td>
<td>11.2</td>
</tr>
<tr>
<td>Adequate bowel preparation quality</td>
<td>97.6%</td>
<td>87.5%</td>
<td>5.9</td>
</tr>
<tr>
<td>Missed appointment / no show</td>
<td>0.0%</td>
<td>15.6%</td>
<td>48.4</td>
</tr>
<tr>
<td>Cancellation &lt;24 h before appointment</td>
<td>0.8%</td>
<td>16.0%</td>
<td>24.8</td>
</tr>
<tr>
<td>Results communicated to patient</td>
<td>100.0%</td>
<td>96.2%</td>
<td>10.1</td>
</tr>
<tr>
<td>Results communicated to PCP</td>
<td>100.0%</td>
<td>48.1%</td>
<td>272.2</td>
</tr>
<tr>
<td>Final recommended rescreening interval</td>
<td>100.0%</td>
<td>82.4%</td>
<td>54.0</td>
</tr>
</tbody>
</table>

Treatment of most CRCs is based on stage of disease

86% of all stage I & II CRCs treated with surgery alone

<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon Cancer</th>
<th>Rectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Surgery only (polypectomy or partial colectomy)</td>
<td>Surgery only (polypectomy, local excision or transanal resection)</td>
</tr>
<tr>
<td>I</td>
<td>Surgery only (polypectomy or partial colectomy with lymph node dissection)</td>
<td>Surgery (above or proctectomy w/ colo-anal anastomosis, other surgical options) Possible radiotherapy if patient not suitable for surgery</td>
</tr>
<tr>
<td>II</td>
<td>Surgery (partial colectomy with lymph node dissection) Possible chemotherapy (typically (5-FU + leucovorin) or capecitibine) Possible radiotherapy</td>
<td>Combination modality (surgery + (neoadjuvant &amp; adjuvant) chemotherapy ± radiation) Chemo options include FOLFOX (Oxaliplatin + 5-FU + leucovorin) or CapeOx (capecitibine + oxaliplatin)</td>
</tr>
<tr>
<td>III</td>
<td>Surgery w/ lymph node dissection + adjuvant chemotherapy (FOLFOX or CapeOx) Possible adjuvant radiotherapy</td>
<td>Combination modality (neoadjuvant chemotherapy + radiation, then surgery + adjuvant/consolidation chemotherapy)</td>
</tr>
<tr>
<td>IV</td>
<td>Systemic chemotherapy (above or FOLFIRI (5-FU + leucovorin + irinotecan) or FOLFOXIRI) ± targeted biologic therapies (e.g., bevacizumab or cetuximab) Possible surgery (diverting colostomy + excise metastases)</td>
<td>Systemic chemotherapy (above or FOLFIRI or FOLFOXIRI) or via hepatic artery infusion) ± targeted biologic therapies + radiation + possible surgery Possible ablation or embolization</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Clinical trials frequently offered Options &amp; treatment goals dictated by local vs. distant recurrence</td>
<td>Clinical trials frequently offered Options &amp; treatment goals dictated by local vs. distant recurrence</td>
</tr>
</tbody>
</table>
Colorectal Cancer Incidence and Mortality Rates, United States.

- 140,250 newly diagnosed CRC cases (U.S., 2018, projected)
- 34.8 ♀ to 45.9 ♂ per 100,000 (U.S., 2010-2014, age-adjusted incidence)
- 50,630 deaths from CRC (U.S., 2018, projected)
- 12.2 ♀ to 17.3 ♂ per 100,000 (U.S., 2011-2015, age-adjusted mortality)


Regional differences in U.S. CRC mortality rates: Decreasing vs. increasing trends

- Decreasing CRC mortality rates in Midwest & Northeast best explained by increasing CRC screening rates.
- Increasing CRC rates (esp. in Mississippi River Delta) may involve other risk factors (e.g., “nutrition transition”).
Colorectal Cancer Incidence (2009-2013) and Mortality (2010-2014) Rates by Race/Ethnicity and Sex, United States

Population-based disparities in U.S. CRC mortality rates are based on divergent trend lines

Trends in Average Yearly Age-, Race-, and Sex-Adjusted Colorectal Cancer Mortality Rates, Separated into Tertiles of High, Middle, and Low Socioeconomic Status at the County Level, 1968–2008.

Regional CRC incidence rates and mortality rates in Mississippi are strongly correlated with colonoscopy rates.

Faruque et al. BMC Res Notes (2015) 8:423
Community-level wealth & per-capita income affects resource distribution

Table 4 Incomes within and beyond 30-min drives to colonoscopy facilities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Within 30-min drives</th>
<th>Beyond 30-min drives</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median household income</td>
<td>33,607</td>
<td>33,953</td>
<td>0.597</td>
</tr>
<tr>
<td>Mean household income</td>
<td>46,291</td>
<td>45,279</td>
<td>0.194</td>
</tr>
<tr>
<td>Per capital income</td>
<td>17,797</td>
<td>17,141</td>
<td>0.049</td>
</tr>
</tbody>
</table>

79% of the state (38% of the population) is beyond a 30-minute drive to gastroenterologist

Table 5 Incomes within and beyond 30-min drives to gastroenterologists’ primary practice sites

<table>
<thead>
<tr>
<th>Variable</th>
<th>Within 30-min drives</th>
<th>Beyond 30-min drives</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median household income</td>
<td>35,058</td>
<td>33,889</td>
<td>0.279</td>
</tr>
<tr>
<td>Mean household income</td>
<td>47,370</td>
<td>45,572</td>
<td>0.083</td>
</tr>
<tr>
<td>Per capital income</td>
<td>18,334</td>
<td>17,294</td>
<td>0.016</td>
</tr>
</tbody>
</table>

52% of the state (17% of the population) is beyond a 30-minute drive to a colonoscopy facility
Divergent CRC incidence trends in post-50 vs. pre-50 y.o. since 1994


NOTE: Ordinate scales on graphs are not equal; magnitude of CRC incidence & mortality very different in age groups shown.
Annual percent change in age-specific rectal cancer incidence rates in the United States, 1974–2013

Increasing trends in 20-54 y.o.

Decreasing trends in age ≥ 55 y.o.

NOTE: Tremendous variation in ordinate scales

Annual percent change in age-specific colon cancer incidence rates in the United States, 1974–2013

**Increasing trends in 20–49 y.o.**

**Decreasing trends in age ≥ 55 y.o.**

**NOTE:** Tremendous variation in ordinate scales

Most sporadic CRCs are driven by accumulation of common mutations with low individual impact; most known familial CRCs driven by rare mutations with high impact.

Genes with predisposing mutations to inherited colorectal cancer syndromes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Hereditary syndrome</th>
<th>Age of onset (years)</th>
<th>Pathway/biological function*</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Familial adenomatous polyposis (FAP), attenuated FAP (AFAP), Gardner syndrome</td>
<td>34–43</td>
<td>Wnt signalling pathway</td>
</tr>
<tr>
<td>MUTYH</td>
<td>MYH-associated polyposis (MAP)</td>
<td>48–56</td>
<td>Base excision repair</td>
</tr>
<tr>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Lynch syndrome</td>
<td>44–56</td>
<td>Mismatch repair</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden syndrome (includes BRR syndrome)</td>
<td>&lt;50 (BRR paediatric onset)</td>
<td>Negative regulator of metabolic signalling</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz-Jeghers syndrome (PJS)</td>
<td>65</td>
<td>Tumour suppressor</td>
</tr>
<tr>
<td>GREM1, 15q13 locus</td>
<td>Hereditary mixed polyposis syndrome (HMPS)</td>
<td>48</td>
<td>TGFβ/BMP signalling pathway</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>HMPS, juvenile polyposis syndrome</td>
<td>48, 42</td>
<td>TGFβ/BMP signalling pathway</td>
</tr>
<tr>
<td>MADH4/SMAD4</td>
<td>Juvenile polyposis syndrome</td>
<td>42</td>
<td>TGFβ/BMP signalling pathway</td>
</tr>
<tr>
<td>POLE, POLD1</td>
<td>Oligopolyposis or polymerase proofreading associated polyposis</td>
<td>23–80</td>
<td>DNA repair</td>
</tr>
</tbody>
</table>

Factors increasing risk for CRC

- **Intrinsic Risk Factors (Non-Modifiable)**
  - Age
  - Ethnicity
  - Family History
  - History of Polyps
  - History of Inflammatory Bowel Disease
  - Central Obesity*
  - Type II Diabetes
  - Specific Genetic Conditions

- **Environmental / Socio-economic Risk Factors**
  - Community-level poverty
  - Lack of Insurance
  - Lack of Access to Medical Care

- **Behavioral Risk Factors (Modifiable)**
  - Non-compliant with screening recommendations
  - Red meat consumption
  - Processed meat consumption
  - Low vegetable, low fiber diets
Thanks to the 70x2020 Colorectal Cancer Screening Partnership for raising awareness throughout Mississippi!

Greenville (4-10-2018)

Jackson (4-31-2018)

Tupelo (4-3-2018)

Biloxi (4-22-2018)
Summary

• CRC cancer biology explains why prevention is highly effective & identifies areas for improvement.
• CRC epidemiology reveals changing landscape of disease.
• CRC in young adults requires attention to symptoms to avoid delays in diagnosis.
• CRC genetic factors can identify young high-risk individuals.
• CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.
• CRC screening options are varied & require colonoscopy for confirmation.
• CRC screening policies benefit to health care system by reducing expensive medical procedures & saving lives.