Natural History and Epidemiology of Colorectal Cancer

Prevent Cancer Foundation
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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.
Learning Objectives

After engaging in this activity, participants will be able to:

1) Describe the population- and geographic-based epidemiological trends in colorectal cancer (CRC) incidence and mortality rates and the probable causes of CRC disparities.

2) List the recommended CRC screening options and their re-screening frequencies.

3) Associate the predominant biological process of colorectal cancer development with the rationale supporting screening strategies for average-risk populations.

4) Assess the impact of intrinsic, behavioral, environmental and socio-economic CRC risk factors.

5) Recommend CRC screening for family members of patients with colorectal cancer due to Lynch syndrome or other genetic factors indicative of above-average cancer risks.

6) Re-examine young adults who present with symptoms of colon cancer or rectal cancer for these diseases.
Fundamental Colorectal Anatomy

Regional lymph nodes provide CRC staging information

SOURCE: National Cancer Institute
Why focus on colorectal cancer?

- CRC is highly preventable & declining in most states.

- CRC is 2\textsuperscript{nd} 4\textsuperscript{th} most common cancer in men + women (USA).
  - 1 in 23 American males; 1 in 25 American females

- CRC is 2\textsuperscript{nd} leading cause of cancer death in men + women (USA).

- CRC treatment costs are 2\textsuperscript{nd} highest of all cancer sites (USA).

- CRC screens are net cost-\textbf{SAVING} (USA).
Global vs. U.S.A. trends in colorectal cancer incidence

Colorectal Cancer Incidence and Mortality Rates, U.S.A.

- 145,600 newly diagnosed CRC cases (U.S., 2019, projected)
- 39.3 per 100,000 (U.S., 2011-2015, age-adjusted incidence)
- 51,020 deaths from CRC (U.S., 2019, projected)
- 14.2 per 100,000 (U.S., 2012-2016, age-adjusted mortality)

Regional differences in CRC mortality rates may reflect decreasing & 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”).

Population-based disparities have significant adverse effect on overall CRC mortality rates in U.S.

Colorectal Cancer Incidence (2009-2013) and Mortality (2010-2014) Rates by Race/Ethnicity and Sex, United States

The CRC screening revolution occurred in 1973


“Polypectomy Via the Fiberoptic Colonoscope — Removal of Neoplasms beyond Reach of the Sigmoidoscope”


by

William I. Wolff, M.D. and Hiromi Shinya, M.D.
If you look inside a colon, what might you see?

- Normal appearance
- Semi-pedunculated polyp
- Sessile polyp
- Villous polyp
- Colon carcinoma
- Obstructing colon mass

Image Source: Malignant Lesions of Colon, by Ira M. Hanan, *Atlas of Colon Pathology; 2015*
Nearly 70 years of progress needed to reach our current understanding of colon and rectal cancers ... and to recognize that an even better understanding is forthcoming

• Early 1950s: Malignant potential of villous adenomas generally recognized, but the adenoma – carcinoma sequence greatly debated.

• Vogelstein et. al. (PNAS, 1988) provide evidence for a progressive model of sporadic colorectal tumorigenesis based on the accumulation of genetic alterations from small adenomas to large adenomas to invasive cancers.
  - These account for the majority of sporadic CRCs which have both structural and numerical chromosomal instability (CIN), and are typically aneuploid.

• Lynch, et. al. (Gastroenterology, 1993) recognized that colon cancers in hereditary nonpolyposis colorectal cancer (HNPCC, a.k.a., Lynch syndrome) were clinically-, genetically-, and histologically-distinct from sporadic CRCs.
  - These are associated with defects in DNA mismatch repair (MMR), resulting in microsatellite instability (MSI), and are typically diploid. While Lynch syndrome accounts for only ~3% of CRCs, ~15% of CRCs show MSI.

• Toyota, et. al. (PNAS, 1999) recognized the CpG island methylator phenotype (CIMP) of CRCs.
A progressive model of sporadic colorectal tumorigenesis:
From normal epithelium to adenomatous polyp to colon/rectal cancer

Foundations / Observations / Assumptions

- Adenoma rare in individuals under 49
- Adenomas & CRC more prevalent in individuals 50 & older.
- Adenoma prevalence increases in the 6th, 7th, and 8th decades of life.
- ~2-5 years from early to advanced adenoma.
- ~2-5 years from advanced adenoma to early cancer.

Ma, et. al. (2016) J Gastroenterol 51:841–852
Preventive CRC screening via colonoscopy & polypectomy:
Predicated on sporadic occurrence & progression of adenoma to carcinoma in “average risk” individuals

- <10% of all adenomas become cancerous, but the vast majority of colorectal cancers develop from adenomas.


### Summary of Colorectal Cancer Risk Factors and Preventive Factors

<table>
<thead>
<tr>
<th></th>
<th>Adverse Risk Factor</th>
<th>Beneficial Preventive Factor</th>
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<tbody>
<tr>
<td><strong>Sociodemographic factors</strong></td>
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<td>Older age</td>
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<td>Male sex</td>
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<td><strong>Medical factors</strong></td>
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<td>Family history</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Helicobacter pylori infection</td>
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<tr>
<td>Other infections</td>
<td>(↑)</td>
<td></td>
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<tr>
<td>Large bowel endoscopy</td>
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<td>(↓)</td>
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<td>Hormone replacement therapy</td>
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<td>(↓)</td>
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<tr>
<td>Aspirin</td>
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<td>Statins</td>
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<tr>
<td><strong>Lifestyle factors</strong></td>
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<tr>
<td>Smoking</td>
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<td>Excess alcohol consumption</td>
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<td>Obesity</td>
<td>(↑)</td>
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<tr>
<td>Physical activity</td>
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<td>(↓)</td>
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<tr>
<td><strong>Dietary factors</strong></td>
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<tr>
<td>High consumption of red and processed meat</td>
<td>(↑)</td>
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<tr>
<td>Fruit and vegetables</td>
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<td>(↓)</td>
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<tr>
<td>Cereal fiber and whole grain</td>
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<td>(↓)</td>
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<tr>
<td>Fish</td>
<td></td>
<td>(↓)</td>
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<td>Dairy Products</td>
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### 2016 U.S. Preventive Services Task Force recommended CRC screening tests

<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</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>

*Positive findings require follow-up colonoscopy.*
Will USPSTF recommend CRC screening to begin at age 45 for average-risk Americans?
<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 capecitbine) Possible radiotherapy</td>
<td>Combination modality (surgery + (neoadjuvant &amp; adjuvant) chemotherapy ± radiation) Chemo options include FOLFOX (Oxaliplatin + 5-FU + leucovorin) or CAPOX (capecitbine + oxaliplatin)</td>
</tr>
<tr>
<td>III</td>
<td>Surgery w/ lymph node dissection + adjuvant chemotherapy (FOLFOX or CAPOX) Possible adjuvant radiotherapy</td>
<td>Combination modality (neoadjuvant chemotherapy + radiation, then surgery + adjuvant/consolidation chemotherapy)</td>
</tr>
<tr>
<td>IV (Clinical trials offered)</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>
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</table>
Not all CRCs develop through the conventional sporadic route: The spectrum of CRC subtypes is evolving.
Different CRC subtypes are associated with varying prognoses.

Multiple classification systems describe the heterogeneity of CRC subtypes. We NEED to transform this into clinically actionable information.


Figure 1. Distribution of CMS by right- and left-sided CRC. Right-side CRC was defined as the cecum through transverse colon, and left-side CRC was defined as the splenic flexure through rectum. Abbreviations: CMS, consensus molecular subtype; CRC, colorectal cancer.
Revised Bethesda Guidelines for Testing Colorectal Tumors for MSI
(Pembrolizumab, an Immune Checkpoint Inhibitor, is now indicated for Lynch syndrome CRCs and other MSI-H / dMMR (defective DNA Mismatch Repair) CRCs)

- Tumors from individuals should be tested for MSI (microsatellite instability) in the following situations:
  - Colorectal cancer diagnosed in a patient who is < 50 years of age
  - Presence of synchronous, metachronous colorectal or other Lynch-associated tumors, regardless of age
  - Colorectal cancer with the MSI-H histology diagnosed in a patient who is < 60 years of age
  - Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumor, with one of the cancers being diagnosed under age 50 years
  - Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch-related tumors, regardless of age

*Lynch syndrome–related tumors include
- Colorectal tumors
- Endometrial tumors
- Stomach tumors
- Ovarian tumors
- Pancreatic tumors
- Ureter and renal pelvic tumors
- Biliary tract tumors
- Brain (usually glioblastoma, as seen in Turcot syndrome) tumors
- Sebaceous gland adenomas
- Keratoacanthomas in Muir-Torre syndrome
- Carcinomas of the small bowel
Distribution of known colorectal cancer genetic susceptibility loci

Distribution of Colorectal Cancer Burden by Age at Diagnosis (U.S.A.)

Early-onset colorectal cancers: An urgent need for improved primary-care provider awareness

<table>
<thead>
<tr>
<th>Characteristic (relative to &gt;50 y.o.)</th>
<th>Cohort size</th>
<th>Statistical confidence</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumors in the distal colon or rectum</td>
<td>4 cohorts totaling 36,000 pts. w/ CRC</td>
<td>P &lt; .0001</td>
<td>Willauer, et. al., (2019)</td>
</tr>
<tr>
<td>Primary tumor site increases in a step-wise fashion from the ascending colon to rectum</td>
<td>369,796 pts. w/ CRC from 2000-2011 SEER</td>
<td>P &lt; 2.2e-16</td>
<td>Yeo, et. al., (2017)</td>
</tr>
<tr>
<td>Synchronous metastatic disease</td>
<td>4 cohorts totaling 36,000 pts. w/ CRC</td>
<td>P = .009</td>
<td>Willauer, et. al., (2019)</td>
</tr>
<tr>
<td>Associated with distant disease</td>
<td>369,796 pts. w/ CRC from 2000-2011 SEER</td>
<td>P &lt; .001</td>
<td>Yeo, et. al., (2017)</td>
</tr>
<tr>
<td>Traditional risk factors (obesity, diabetes, smoking, excess alcohol consumption) NOT associated with early-onset CRC</td>
<td>369,796 pts. w/ CRC from 2000-2011 SEER</td>
<td>P = 0.006, 0.5812, 0.6465, and 0.6649, respectively</td>
<td>Yeo, et. al., (2017)</td>
</tr>
<tr>
<td>Difference in Consensus Molecular Subtype (CMS) distribution, with markedly higher prevalence of CMS1 in early-onset CRCs</td>
<td>626 patients</td>
<td>P = 0.0003</td>
<td>Willauer, et. al., (2019)</td>
</tr>
</tbody>
</table>

Sources:
Summary

• CRC epidemiology reveals changing landscape of disease.

• CRC screening options are varied & require colonoscopy for confirmation.

• CRC cancer biology explains why prevention is highly effective for average-risk individuals.

• CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.

• CRC genetic factors can identify high-risk individuals in affected families and may be useful in treatment decisions.

• CRC in young adults requires attention to symptoms to avoid delays in diagnosis.

• The elimination of deaths caused by CRC will require additional translational and clinical research, and improvements in health care systems and policies.
Thank you for your attention. Any questions?