Colon Cancer Screening: An Update
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Disclosures
• Nothing to disclose.

Lecture Overview
• Introduction/Background
• Who should get screened
  • Average Risk patients
  • Lynch Syndrome
  • Screening in African Americans
  • Screening in the Elderly
  • Screening in Young patients
• How to Screen
  • FIT v gFOBT
  • CT Colonography
  • DBCE
  • Stool DNA testing
  • The Best Test?
  • New Biomarkers?

Background
• CRC is 2nd leading cause of cancer death in US
• 8% of all new cancer cases in US annually
• Adults in US have a lifetime CRC risk of ~5%
• Most frequently diagnosed: 65 - 74 years
• Median age at death: 68 years
• Estimated 135,000 new cases of CRC
• Estimated 50,000 deaths related to CRC

Who to Screen?
• “Average Risk”: 50–75 (USPSTF, 2008, 2016)
    (* 45 for all AA)
• https://www.cancer.gov/colorectalcancerrisk/
  – Calculates person’s 5 yr, 10 yr, and lifetime risk
  – Takes into consideration age, gender (M>F), race (AA>white),
    diet (red meat, low veg), lifestyle (tobacco, obesity, exercise, etc)
    in addition to family history (2-6X increased risk)

Background
• 5 year survival: 90% if localized to colon
• 68% for regional disease (local LN)
• only 10% if distant mets
• CRC incidence and mortality rates declining over past 2 decades
  – Attributed to CRC screening/early detection
  – Between 2004 - 2013, CRC incidence declined at average annual rate of 3% per/yr
  – CRC mortality declined at average annual rate of 2.7% per/yr
• As of 2012, ~28% of eligible adults still not screened.
Lynch Syndrome

- 70-80% CRC sporadic w/o inherited pattern
  - 20-30% a potential inherited component
- Lynch Syndrome: MC
  - 1966, Dr Henry T Lynch noted family cluster of CRC w/ stomach/endometrial tumors
  - ~3% of all new CRC
  - Early 1990s, DNA mismatch (MMR) implicated
  - AD inheritance pattern
  - Mean age at CRC diagnosis: 44 – 61

Table 3. Gene-specific cumulative risks of colorectal cancer by age 70 years in Lynch syndrome

<table>
<thead>
<tr>
<th>Gene mutation carriers</th>
<th>Risk, %</th>
<th>Mean age at diagnosis, y</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic cancer</td>
<td>5.5</td>
<td>69 (29)</td>
<td></td>
</tr>
<tr>
<td>MLH1/MSH2 Male: 27-74</td>
<td>27-46</td>
<td>(17-21,23)</td>
<td></td>
</tr>
<tr>
<td>Female: 22-53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>22</td>
<td>Male: 22</td>
<td></td>
</tr>
<tr>
<td>Female: 10</td>
<td>54-63</td>
<td>(17,22)</td>
<td></td>
</tr>
<tr>
<td>Male and female: 18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM22</td>
<td>20</td>
<td>Male: 20</td>
<td></td>
</tr>
<tr>
<td>Female: 15</td>
<td>47-66</td>
<td>(29)</td>
<td></td>
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Table 1. Revised Bethesda Guidelines

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>References</th>
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<tr>
<td>CRC diagnosis at age &lt;50 years</td>
<td>99%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>Presence of synchronous or metachronous CRC or other (associated cancers)</td>
<td>99%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>CRC with MSI high with associated features (osteosarcoma, melanoma, Ewing's sarcoma, melanoma, lymphoma)</td>
<td>99%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>Presence of adenomatous polyposis in first degree relative (at age &lt;50 years)</td>
<td>99%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>Tumor suppressor gene mutation in first degree relative</td>
<td>99%</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>Presence of synchronous or metachronous CRC or other (associated cancers)</td>
<td>99%</td>
<td>99%</td>
<td></td>
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Figure 3. The pre-procedural Colorectal Cancer Risk Assessment Tool

- Correctly identified 95% of individuals with germline mutations causing LS.
- Cumulative Sensitivity – 77%


Screening in Lynch Syndrome

- Every 1-2 years persons at risk (first-degree relatives of those affected) or affected with LS beginning @ ages 20 – 25 years
  - or 2–5 years before the youngest age of diagnosis of CRC in the family if diagnosed < 25 years.

ASA and Lynch

- AGA (2014 guidelines): ASA should be offered for CRC prevention
- Burn et al (Cancer 2011; 378: 2081)
  - The Colorectal Adenoma/carcinoma Prevention Program (CAPP)-2
  - Prospective, randomized, double blind to assess effect of ASA on CRC incidence (LS secondary)
Screening in African Americans

• AGA (2008): screening beginning @ age 45
  – Based on ACG Committee on Minority Affairs and Cultural Diversity from 2005
  – ASGE followed suit in 2010
  – ACS, USMSTF, and ACR postponed due to lack of evidence on affect on screening/survival
• Paquette et al. (Gastroint Endosc. 2015;82(5):878)
  – Retrospective SEER database (2000-2011) review
  – Calculate age-specific incidence in AA and calculate joinpoint.

Screening in African Americans

• While age of screening changed, are clinicians actually referring for CRC screening?

• May et al (Am J Gastroenterol. 2015;110(10):1388) examined association between patient race and provider recommendation for CRC screening

Screening in The Elderly

• USPSTF: CRC screening to age 75 (Grade A)
  – No change from 2008 guidelines
• Adults 76-85: decision to screen individualized (Grade C)
  – Net benefit is small
  – Those never screened more likely to benefit
  
<table>
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<tr>
<th>2016</th>
<th>2018</th>
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<tr>
<td>Adult age 65 or more</td>
<td>Adult age 76 or more</td>
</tr>
<tr>
<td>Direct colonoscopy</td>
<td>Direct colonoscopy</td>
</tr>
<tr>
<td>Grade C</td>
<td>Grade C</td>
</tr>
<tr>
<td>Grade D</td>
<td>Grade D</td>
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Screening in the Elderly

- USPSTF (2016): Screening most appropriate for those healthy enough to withstand treatment
  - Also takes into consideration comorbidities
- What’s more important: age or comorbidities?
    - NCI funded population-based, longitudinal cohort study of ~ 850,000 patients
    - Comorbidity measured using the Charlson index
  - Likelihood of being up to date with CRC screening was significantly lower for patients aged >76 years than < 75 (p<0.001).
  - Comorbidity was less influential than age

Young Age Screening?

- CRC: ~ 15% of patients are younger than 50.
- Guidelines not yet suggesting screening before 50 (exception: ACG  screening @ 45 for AA)
  - USPSTF 2016: due to modest increase in life-years gained by starting screening earlier, and lack of empirical evidence in younger populations, do not suggest reducing screening age
- CRC rates and all cause mortality declining due to improved screening, except for those < 50

Evidence of CRC in young

  - SEER database (1973-1999) compared incidence rates for two age groups: young patients (20-40 years, n = 5383) and older patients (60+ years, n = 256,401)
  - Young: colon cancer incidence increased 17% to 2.1 (P < 0.05), and rectal incidence increased 75% to 1.4 (P < 0.05)
  - Younger patients also had less localized CRC and higher rates of poorly differentiated CRC
  - Retrospective cohort study (SEER database) of patients age 20+ diagnosed with invasive CRC from 1974 - 2013

Specific Populations

- Smokers:
  - Associated with ~20 % of all CRCs in the US
  - 20+ pack-years have over 2 ~ 3 X the risk for colorectal adenomas vs non-smokers
  - 30 % increased risk for colon and rectal cancer in male and female smokers
  - ACG (2008): Initiation of screening at a younger age (as early as 45 years) may be shown to be beneficial and cost-effective in persons with more 20 pack-years of smoking.
Specific Populations

- Obesity:
  - Risk of CRC for obese patients vs non-obese patients is increased by 1.5 – 2.8X
  - However, BMI was related to CRC risk for younger (50 – 66 years) but not older (age 67 – 71 years)
  - BMI associated w/ increased risk of colon, but not rectal cancer
  - ACG (2008): Initiation of screening at an earlier age (as early as 45 years) may be beneficial and cost-effective in obese patients.

How to Screen

- In general, 2 broad categories:
  - Stool based (FIT, gFOBT, DNA)
  - Structural based (colonoscopy, FS, DCBE, CTC)

How to Screen

- Stool tests:
  - USPSTF Guidelines on CRC Screening
    - 2008 guidelines: screening with colonoscopy every 10 years, annual FIT/gFOBT, or flex sig every 5 years with gFOBT every 3 years.
      - No mention of CTC or DNA due to lack of evidence
  - Changes to 2016 edition: Does not state any specific modality.
      - No “one size fits all” approach
      - More concerned about access to screening
      - Added recommendations on CTC and DNA testing

USPSTF Update: 2016

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ACG and ASGE Guidelines

- ACG and ASGE guidelines removed gFOBT in favor of FIT
- ASGE: updated guidelines on FIT testing in 2017
  - 2014 meta-analysis (19 studies): pooled sensitivity 79% and specificity 94% for CRC
    - Subgroup analysis (colonoscopy as reference standard):
      - Overall sensitivity and specificity of 1-time FIT was 77% and 94%, respectively
    - Hassan et al (Aliment Pharmacol Ther 2012;36:929) meta-analysis:
      - FIT superior to gFOBT both for CRC detection (RR, 1.96) and advanced neoplasia (RR, 2.28)
Updates on FIT

- At least 4 RCTs and 2 meta analyses showed increased adherence of FIT to gFOBT
  - 20% improved adherence
  - Due to need for fewer samples and no dietary restrictions
- FIT and ASA/NSAID/anticoagulant use:
  - 2 prospective studies (Ann Gastroenterol 2009;104:503; JAMA 2010;304:313-20): improved sensitivity with no change in specificity

Fecal DNA Testing

- Has been studied since 1990s (Sidransky, et al identified ras mutations in stool, 1992)
- 1st generation DNA testing:
  - Better than gFOBT (Imperiale, et al, 2004)
  - Limitations: DNA degradation, lack of buffers, limited marker panels.
- 2nd generation DNA testing:
  - 4 methylated genes, KRAS, alpha-actin DNA panel

Fecal DNA Testing

  - 385 cases (252 with CRC and 133 with an adenoma >1 cm) and 293 controls with normal colonoscopy
  - Using 90% as cut-off

Fecal DNA Testing: Cologuard

- Imperiale et al (2014):
  - Asymptomatic persons b/w 50 - 84 yo considered to be at average risk for CRC
  - Exclusion:
    - personal history of colorectal neoplasia or digestive cancer
    - IBD or colon resection (except for sigmoid diverticula)
    - Colonoscopy within the previous 9 years or a barium enema
    - CT colangiography or sigmoidoscopy in the previous 5 years
    - Positive FIT or gFOBT in previous 6 months
    - Overt rectal bleeding within the previous 30 days
    - Personal or family history of CRC
Specificity among participants with non-advanced or negative findings:
DNA: 86.6%  FIT: 94.9% (P<0.001)

Specificity in those with negative results on colonoscopy:
DNA: 89.8%  FIT: 96.4% (P<0.001).

What’s the best test?

Quality Markers

- ADR: >25% men and >15% women ≥ 50 years.

Biomarkers

- Circulating methylated SEPT9 DNA:
  - Methylation known to occur in cancers, including CRC
  - SEPT 9 DNA in CRC known since 2009
  - FDA approved blood DNA test in 2016
- Church et al: multicenter, prospective study examining methylated SEPT 9 DNA in >7000 patients undergoing CRC screening.
  - standardized sensitivity of 48.2%
  - CRC stages I-IV, values were 35.0%, 63.0%, 46.0% and 77.4%, respectively; for advanced adenomas, 11.2%
  - Specificity: 91.5%

Biomarkers: RNA

- Fecal RNA is not as extensively studied due to degradation in stool.
- Some studies, but shift changed to fecal miRNA
  - MiRNA: ~22 nucleotide noncoding RNA molecules
  - Koga et al: miR-17-92 cluster and miR-135 was significantly higher in CRC patients vs. healthy volunteers (p<0.0001)
  - Link et al: higher miR-21 and miR-106a levels in patients with adenomas and CRCs compared with control (P<0.05)
- What about serological/serum MiRNA?
Biomarkers: Serum RNA

- Dandachi et al: blood cytokeratin 20 (CK20) mRNA levels significantly higher in CRC patients vs. control (P = 0.001)
  - But no difference in CRC v IBD patients
- Huang et al: measured 12 serum miRNA in CRC v healthy controls
  - Of the 12, miR-29a and miR-92a had significant diagnostic value.

ROC curve analysis:
- MiR-29a: 0.844 and miR-92a: 0.838 in discriminating CRC from controls
- Could also discriminate advanced adenomas from controls and yielded an AUC of 0.769 for miR-29a and 0.749 for miR-92a.

Biomarkers: Other markers

- Stool M2 isoform of pyruvate kinase (M2-PK): found in highly proliferating cells.
- Koss et al: stool M2-PK in 13 controls vs 32 CRC
  - Median levels: 1.75 U/ml in control group; 1.2 U/ml in polyps < 10 mm; 5.32 U/ml in polyps > 10 mm (P = 0.041 vs control); 11.72 U/ml in CRC (vs control group, P = 0.0001; vs patients with polyps, P = 0.02)
  - Sensitivity (level < 3.33 U/ml): 91% CRC, 60% for >10 mm, 20% for <10 mm polyps
  - Specificity: 92% for CRC (100% if cut-off 4 U/ml)

Take Home Points

- Colonoscopy still the gold standard
- Look out for alarm symptoms in “young” patients