Emerging Concepts in Colorectal Cancer Screening

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Colon Cancer (CRC)

- 2\textsuperscript{nd} most common cause of cancer death in North America
- Over 148,000 patients newly diagnosed per year
- 49,960 deaths per year
- Incidence and Mortality has decreased
  - screening rates have increased
- Barriers to screening:
  - lack of health insurance
  - lack of awareness
  - lack of recommendation by health care provider
  - lack of transportation
Stages of CRC and Outcomes

- CRC survival 5 years
  - 90% localized to the bowel
  - 68% Locoregional with nodes
  - <20% if distant spread
Goals of Screening

- Medical Definition: A test to identify and eliminate those who are not affected by a disease.
- Reduce Mortality from Colon Cancer
  - Early Detection: find it earlier
  - Prevention
    - Stop it from happening
      - Find precursor lesions and reduce incidence of future cases
Colorectal Cancer Screening Tests

Fig. 2. Different biomarkers and their role in tumor evaluation
IBD

- Crohn’s Disease and Ulcerative Colitis are at increased risk for CRC
  - start with 8 year history of disease
  - Flat dysplasia

*Figure 1.* Endoscopic photograph of characteristic pseudopolyps: multiple, with smooth surface, sharp borders.

*Figure 3.* Endoscopic photograph of a characteristic dysplastic polyp in colitic mucosa: irregular borders, dull surface, solitary.
Family History of Colon Cancer

- Possible hereditary syndrome if
  - CRC <50
  - multiple family members with CRC
  - Familial Polyposis
  - Lynch Tumors
    - Uterine, gastric, ovarian, small bowel, pancreas
Hereditary Colon Cancer syndromes

- **NONPOLYPOSIS**
  - Lynch Syndrome (HNPCC)
    - 3% of all CRC

- **POLYPOSIS**
  - Familial Adenomatous Polyposis (FAP)
    - 1% of all CRC
  - MYH-Associated Polyposis (MAP)
Intervals from polyp to Cancer

Accelerated progression from adenoma to cancer

General Population 5-10 years

Lynch Syndrome 1-3 years

0 5y 10y
Types of CRC Screening Tests

- Structural: CT colonography, Sigmoidoscopy, Colonoscopy
- Stool based tests
  - FOBT, FIT, DNA tests
## Targets of Screening Methods

<table>
<thead>
<tr>
<th>Test</th>
<th>Cancer</th>
<th>All Polyps</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOBT</td>
<td>Yes</td>
<td>NO</td>
<td>Annual</td>
</tr>
<tr>
<td>FIT</td>
<td>Yes</td>
<td>NO</td>
<td>Annual</td>
</tr>
<tr>
<td>Stool DNA</td>
<td>Yes</td>
<td>NO</td>
<td>Not Known</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>L colon</td>
<td>L colon</td>
<td>5 years</td>
</tr>
<tr>
<td>CT colonography</td>
<td>Yes</td>
<td>No</td>
<td>5 years</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Yes</td>
<td>Yes</td>
<td>10 years</td>
</tr>
</tbody>
</table>

Rationale of CRC prevention

- Find the precursors and remove them
- Endpoint for CRC is Advanced Adenoma
  - Studies of
    - Prevention and Nutrition
    - Detection
      - Advanced Adenoma
        - Villous histology
        - High grade dysplasia
        - Size of 1 cm or greater
Approved Methods for Screening by US MultiSociety Task Force on CRC

- Multiple CRC Approved methods
  - Early detection (FIT, FOBT)
  - Detect and prevent by removal of adenomatous polyps (CT colonography, colonoscopy).
- Group recommended the primary goal is prevention.
  - Tests that detect and remove early cancers and advanced polyps should be encouraged.
Stool tests

- FOBT-detects peroxidase activity of heme
  - Hemoccult Sensa one time sensitivity of CRC <75%
    - Multiple stool samples are required
    - Hold Aspirin, NSAIDS, vitamin C, red meat

- FIT-Fecal Immunochemical Tests
  - Antibodies bind to human hemoglobin
  - One time sensitivity for CRC of 60-85%
    - No dietary restrictions
Stool Testing Summary

- Randomized control trials > 10 years
  - reduction in death from colon cancer of 15-33%
- Small polyps do not bleed
  - detection of adenomatous polyps is limited
- Repeat testing is needed
  - Polyps and cancers bleed intermittently
  - Poor test sensitivity but good program sensitivity
    - failure to complete up to 40%
- A positive test should always lead to colonoscopy
  - Don’t try to explain it away
  - 30% of physicians came up with some other plan
- Not office based procedure
  - No fingers
CT colonography

- Undergo a bowel preparation
- Ingest a small amount of water soluble contrast
- Lie in the CT scanner and a tube is inserted into the rectum
- Air distends the colon
- Patient is scanned in different positions
  - On back then on stomach
CT Colonography

- Detection of Polyps >10mm
  - superior to barium enema
  - Up to 90%
    - probably as good as colonoscopy
- Requires a bowel preparation
- No sedation, insignificant risk
- polyps→colonoscopy
CT colonography

- Accuracy to detect is limited in smaller polyps
- 15-25% of patients screened by CT colonography would need to be referred for colonoscopy
- American College of Radiology: Endorsed for those without strong family history
  - Average risk screening
  - Not indicated in:
    - Pregnancy, evaluation of anal disease, IBD
Controversies in CTC for CRC screening

- Extracolonic findings
- Followup of small polyps.
  - Likelihood of advanced histology in small (<6mm) polyps in <2%.
  - >6mm go to colonoscopy
    - <6mm may get repeat ct colonography in 5 years
- Polyps less than 6 mm may not be reported.
- False positive results up to 15%
Sigmoidoscopy

Direct exam of distal colon
- Require a bowel preparation
- Can be performed well by non-GI providers
- Advanced proximal neoplasia is missed
  - >30% of advanced neoplasia
- Proximal neoplasia
  - more common in women and those >60 years old.
- Reduces significantly colorectal cancer mortality in the left colon
Detection Rates of Screening Tests for Cancer and Advanced Adenomatous Polyps

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>One time Sensitivity for CRC</th>
<th>One time Sensitivity for Advanced Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOBT</td>
<td>50-75%</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>FIT</td>
<td>60-85%</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Stool DNA testing</td>
<td>&gt;80%</td>
<td>40%</td>
</tr>
<tr>
<td>CT colonography</td>
<td>&gt;90%</td>
<td>90%</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>95%</td>
<td>88-98%</td>
</tr>
</tbody>
</table>
Colonoscopy

- Quality of colonoscopy depends on:
  - Bowel preparation
  - Patient tolerance
  - Endoscopist
- Interval cancers occur
  - Incomplete polyp resection
  - Missed lesions
  - Aggressive lesions
- Benefit of colonoscopy
  - National polyp study reduced incidence of CRC by 76-90%
  - Other studies have shown lower rates of prevention
Protection from CRC by Colonoscopy

- Mortality reduction by colonoscopy (Canadian), 67% reduction of left sided CRC
  - Non-significant reduction in mortality of right sided CRC

- Advanced adenomas at follow-up colonoscopy (German)
  - 67% reduction in left sided
  - No reduction in right sided

- Colonoscopy benefit reduced in right side of colon
  - Biology of lesions
    - Flat, more aggressive
    - Failure to detect and remove them
Colonoscopy Limitations

- Requires a bowel preparation
  - Usually perceived as most unpleasant part
- Usually done with sedation
- Patients need transportation
- Miss a day of work
- Requires a chaperone
- Variability in protection from incident cancers
- Operator dependent
- Small Risk of bleed and perforation
- Current reimbursement rewards volume of colonoscopies not performance
Quality in Colonoscopy

- Reporting Indicators:
  - Indication for procedure
  - Appropriate interval if surveillance
  - Bowel Prep Quality
  - Completeness of Exam
  - Polypectomy technique
  - Followup communication
Risks of Colonoscopy

- **Bleeding and perforation**
  - Rates of both vary
  - Can be estimated 1-2/1,000

- **Complications more likely**
  - Elderly
  - Bleeding on antiplatelets and anticoagulants

- **No indication for endocarditis prophylaxis or antibiotics relevant to colonoscopy**
Performance Indicators

- Quality of Bowel Preparations
- Cecal Intubation rates
- Adenoma Detection Rates
- Polyp Retrieval rates
- Unplanned or adverse events
- Followup recommendations
- Withdrawal time greater than 6 minutes
  - Surrogate for adenoma detection rate
Gender and CRC Screening

- Women have a lower age-adjusted risk of CRC and advanced adenoma
  - Lag time of 7-8 years
  - CRC risk
    - 50 year old Man =
    - 58 year old Woman
  - Hormonal delay of CRC from menopause.
  - ACS-MSTF argued against customization of guidelines.
Race and CRC Screening

- African Americans have higher CRC incidence
  - Access to care reduced
  - Failure of physicians to recommend screening
  - Biologic hypothesis
    - Higher age adjusted rates of large polyps

- One group of experts recommended that African Americans start screening at age 45.
  - ACS-MSTF- against customization by race of guidelines
## Risk and USMSTF Recommendations for Screening Intervals Based on Family History

<table>
<thead>
<tr>
<th>Familial Risk Category</th>
<th>Risk Vs. Population</th>
<th>Recommendations Polyps and CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2\textsuperscript{nd} or 3\textsuperscript{rd} degree relative with CRC</td>
<td>1.5X risk</td>
<td>Same as average risk</td>
</tr>
<tr>
<td>1\textsuperscript{st} degree relative with CRC &gt;60 years</td>
<td>2-3 X risk</td>
<td>Begin at 40 years, same interval</td>
</tr>
<tr>
<td>single first degree relative with CRC &lt;60</td>
<td>3-4X</td>
<td>Colonoscopy q5 years, begin at 40 or 10 years younger than earliest case.</td>
</tr>
</tbody>
</table>
### Surveillance of Colorectal Polyps

<table>
<thead>
<tr>
<th>Type of Polyp</th>
<th>Surveillance Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small hyperplastic polyps</td>
<td>Treat like average risk</td>
</tr>
<tr>
<td>1 or 2 small adenoma</td>
<td>5-10 years after the initial polypectomy</td>
</tr>
<tr>
<td>3 to 10 adenoma</td>
<td>3 years after polypectomy</td>
</tr>
<tr>
<td>&gt;10 adenoma</td>
<td>&lt;3 years after polypectomy</td>
</tr>
<tr>
<td>Advanced Adenoma (&gt;1cm, villous, hgd)</td>
<td>3 years after polypectomy</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>One year if complete colonoscopy at time of diagnosis. If incomplete at diagnosis within 3 months of surgery.</td>
</tr>
<tr>
<td>Piecemeal resection of polyp</td>
<td>2-6 months to survey site</td>
</tr>
</tbody>
</table>
Polyp Assessment

Determine if Adenoma is Advanced

- Size
  - 1cm or greater
- Degree of Dysplasia
  - High grade
- Histology
  - Villous
- Number of Polyps
  - 3 or more
DNA testing in Stool

- Sensitivity of 90% for CRC
- DNA mutations in patients with large polyps and colon cancer are shed into stool and can be amplified.
  - KRAS, Methylation markers
- Not dependent upon bleeding
- Issues
  - Clinical relevance of positive DNA test without finding lesions
  - Future direction to screen for other gi malignancies at same time
- Requires further testing in screening cohorts
Novel Methods for Screening for CRC

Table 1. Ideal Features of a Noninvasive Screening Test for Colorectal Neoplasia

<table>
<thead>
<tr>
<th>Features</th>
<th>Beneficial effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly sensitive</td>
<td>Reduces cancer mortality</td>
</tr>
<tr>
<td>For curable-stage cancer</td>
<td>Prevents cancer</td>
</tr>
<tr>
<td>For advanced</td>
<td></td>
</tr>
<tr>
<td>precancerous lesions</td>
<td></td>
</tr>
<tr>
<td>Highly specific</td>
<td>Reduces program cost</td>
</tr>
<tr>
<td>User friendly</td>
<td>Increases appeal/compliance</td>
</tr>
<tr>
<td>Affordable</td>
<td>Increases acceptance/compliance</td>
</tr>
<tr>
<td>Widely distributable</td>
<td>Increases availability/compliance</td>
</tr>
</tbody>
</table>

Ahlquist, D. Gastroenterology 2010;138:2121
## Methods to Detect CRC Noninvasively

**Table 2. Candidate Stool, Blood, and Urine Tumor Markers for the Noninvasive Detection of Colorectal Neoplasia**

<table>
<thead>
<tr>
<th>Stool</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhaged</td>
<td>In circulating tumor cells</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>RNA, DNA, proteins</td>
</tr>
<tr>
<td>Plasma proteins</td>
<td>In circulating phagocytes</td>
</tr>
<tr>
<td>Secreted</td>
<td>RNA, DNA, proteins</td>
</tr>
<tr>
<td>Mucins</td>
<td>In plasma/serum</td>
</tr>
<tr>
<td>Metalloproteinases</td>
<td>DNA</td>
</tr>
<tr>
<td>Exuded</td>
<td>Mutated genes</td>
</tr>
<tr>
<td>Leukocyte proteins</td>
<td>Methylation genes</td>
</tr>
<tr>
<td>Plasma proteins</td>
<td>Proteins</td>
</tr>
<tr>
<td>Exfoliated</td>
<td>Urine</td>
</tr>
<tr>
<td>Fecal whole colonocytes</td>
<td>DNA</td>
</tr>
<tr>
<td>DNA</td>
<td>Mutated genes</td>
</tr>
<tr>
<td></td>
<td>Methylation genes</td>
</tr>
<tr>
<td></td>
<td>Long (nonapoptotic) DNA</td>
</tr>
<tr>
<td></td>
<td>RNA (gene expression)</td>
</tr>
<tr>
<td></td>
<td>Tumor-derived proteins</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
</tr>
<tr>
<td></td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td>Mutated genes</td>
</tr>
<tr>
<td></td>
<td>Nucleosides</td>
</tr>
<tr>
<td></td>
<td>Proteins</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>

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# Pros and Cons of Different Screening Methods for CRC

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOBT, FIT</td>
<td>Cost low, done home, easy</td>
<td>Limited sensitivity and prevention, need to be done yearly</td>
</tr>
<tr>
<td>Stool DNA</td>
<td>Accurate for CRC</td>
<td>Cost, Limited prevention, intervals unknown</td>
</tr>
<tr>
<td>CT Colonography</td>
<td>Sensitive &gt;10mm polyps, Noninvasive</td>
<td>Cost, requires bowel prep, limited sensitivity for &lt;6mm polyps, intervals uncertain</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>Office based, 60% ↓ in mortality in left side CRC, combine with stool tests</td>
<td>Not detect right sided lesions, Less effective older age, women</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>90% Sensitive for advanced adenoma, CRC</td>
<td>Requires bowel prep, expertise, up to 3-5/1,000 serious adverse events.</td>
</tr>
</tbody>
</table>
CRC Recurrence

- COST Clinical Outcomes After Surgical Therapy
- Method of First Detection of Recurrence
  - CEA 29%
  - CT 23%
  - CXR 7%
  - Colonoscopy 13%
  - Longer survival if were able to resect recurrence

Summary

- Screening rates now are inadequate and significant reductions in CRC incidence and mortality are limited by our current rates of screening.
- Both structural and stool based tests when applied in a systematic way can reduce colorectal mortality.
- Stool testing of blood (FOBT, FIT)
  - Limited prevention benefit
  - Any positive test should go to colonoscopy
  - Requires repeating at regular intervals
- Histology and size determine the clinical importance of polyps found.
- CT colonography has ability to detect polyps of over 1 cm with the accuracy comparable to colonoscopy
  - CT colonography has limited ability to detect smaller polyps
- Colonoscopy shows a higher reduction in CRC incidence than any other modality.
- Colonoscopy is dependent on a number of factors: including bowel preparation, operator ability to detect and remove polyps, its benefit in the right colon is questioned.
References

References