Colorectal Cancer Prevention and Early Detection
April 29, 2010

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Chief Cancer Control Officer
Arizona Cancer Center

Common Causes of Cancer Death
*Clin Cancer Res* 15: 5622-5655 (2009)

- Non-Hodgkin's lymphoma
- Liver & intrahepatic biliary
- Ovarian
- Gastric
- Bladder
- Brain
- Kidney
- Myeloma
- Acute myeloid leukemia
- Melanoma

Cancer Deaths from Smoking

- Est. 450 million deaths globally, 2000 to 2050
- Cessation before middle age avoids >90% of lung cancer mortality
- Aggressive tax policy is effective (France)
- Steep increases in smoking in low- and middle-income countries
- Effective treatments for tobacco dependence ARE available
## Cancer Statistics, 2009


<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Estimated New Cases</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>219,440</td>
<td>159,390</td>
</tr>
<tr>
<td>Colorectal</td>
<td>146,970</td>
<td>49,920</td>
</tr>
<tr>
<td>Breast</td>
<td>194,280</td>
<td>40,610</td>
</tr>
<tr>
<td>Prostate</td>
<td>192,280</td>
<td>27,360</td>
</tr>
</tbody>
</table>

## Colorectal Cancer Staging and Time Trends

- **Mucosa**
- **Submucosa**
- **Muscularis propria**
- **Serosa**

- **Dukes**
  - Dukes A: 1
  - Dukes B: 2
  - Dukes C: 1
  - Dukes D: 3

### 5-Year Survival (%) According to Stage

1. Localized – >80%
2. Regional – ~30 to ~70% (no. of nodes)
3. Distant – <10%

- **Lymph node**
- **Liver**
Colorectal Cancer Staging

Clinical | TNM
---|---
Localized | I: Primary tumor within bowel wall
| T1-2, N0, M0
Regional | II: Primary tumor penetrates bowel wall (IIIA), & invades other organs (IIIB) without nodes
| T1-4, N0 (II) or 1 (III), M0
| III: Within bowel wall + nodes (IIIA), penetrates bowel + nodes (IIIB or C)
| T1-4, N1-2, M0
Distant | IV: Distant metastases
| T (any), N (any), M1

Colorectal Cancer Incidence and Mortality 1975-2006


CRC Trends: Incidence (A) & 5-y Survival (B)

# Take Home Message #1

Disparities in access to colorectal cancer prevention and screening measures must be eliminated
- African Americans
- Native Americans
- Hispanics

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## Age-Standardized Colorectal Cancer Incidence and Mortality

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Af. Am.</th>
<th>As./PI</th>
<th>Al/AN</th>
<th>Hisp.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>64.1</td>
<td>72.4</td>
<td>57.2</td>
<td>37.5</td>
<td>49.8</td>
</tr>
<tr>
<td>F</td>
<td>46.2</td>
<td>56.2</td>
<td>38.8</td>
<td>32.6</td>
<td>32.9</td>
</tr>
</tbody>
</table>

|       |       |         |        |       |       |
| **Mortality** |       |         |        |       |       |
| M     | 25.3  | 34.6    | 15.8   | 18.5  | 18.4  |
| F     | 17.5  | 24.6    | 11.0   | 12.1  | 11.4  |

*Ward et al. CA Cancer J Clin 54, 78-93 (2004)*
• ~50% of US population have adenoma(s) by 70 yo
• ≤10% of adenomas are at risk of progression to CRC
Advanced Colorectal Neoplasia

Advanced Adenoma
- ≥ 10 mm
- Villous
- High-grade dysplasia

Muscularis mucosa

Localized cancer

Advanced Colorectal Neoplasia: Prevalence in Screened Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman</td>
<td>Male veterans</td>
</tr>
<tr>
<td>Schoenfeld</td>
<td>Females, military</td>
</tr>
<tr>
<td>Regula</td>
<td>Age 50-66 y</td>
</tr>
<tr>
<td>Regula</td>
<td>Age 40-49 y</td>
</tr>
<tr>
<td>Kim</td>
<td>Healthy screening cohort</td>
</tr>
</tbody>
</table>

Metachronous Colorectal Adenomas

Martinez ME. Gastroenterology 136, 832-841 (2009)

Following removal of all adenomas, metachronous (i.e., new or recurrent) adenomas are found in 20-50% of individuals at surveillance colonoscopy performed 3-5 years later.

Individuals at greatest risk for metachronous adenomas and progression to colorectal cancer can be identified from incident/baseline adenoma characteristics:
- An advanced adenoma (or prior colorectal cancer)
- More than 2 non-advanced adenomas
- Flat adenomas & right-sided adenomas
Take Home Message #2

Not all colorectal adenomas are equal
- Prior colorectal cancer
- Advanced adenomas
- Multiple adenomas
- Flat adenomas and right-sided lesions

COLORECTAL CANCER RISK STRATIFICATION

Colorectal Cancer and Inheritance

Sporadic Cases approximately 66%
HNPCC 2% to 3%
Hamartomatous Polyposis Syndrome < 0.1%
FAP < 1%
Other Inherited, approximately 30%
Take Home Message #3

Every first-degree relative of a patient with colorectal cancer should be aware of this risk factor:
- Number of cases
- First degree (parent, sibling or child) or not
- Age(s) at first diagnosis

Gastrointestinal Diseases Predisposing to CRC

Gastroenterology 138, 746-774 (2010)

- Ulcerative colitis
- Crohn’s colitis

Take Home Message #4

Every patient with a condition that puts them at increased risk for colorectal cancer should be aware of this:
- Ulcerative colitis
- Crohn’s colitis
Sporadic Colorectal Cancer

- Sporadic Cases: approximately 66%
- Other Inherited: approximately 30%
- HNPCC: 2% to 3%
- FAP: < 1%
- Hamartomatous Polyposis Syndrome: < 0.1%

Obesity Trends

- www.cdc.gov/obesity/data/trends.html

- Men and Women obesity prevalence trends from 1960 to 2000

Physical Activity, BMI and Colorectal Cancer

- Up to 50% ↓ in risk for colon cancer with physical activity
- Recent evidence suggests similar effect on rectal cancer risk
- At low levels of physical activity, obesity may ↑ risk for colon cancer
- Less evidence that obesity influences rectal cancer risk
Increased Risk for CRA Recurrence

<table>
<thead>
<tr>
<th>Obesity</th>
<th>Inc. of [gluc] &amp; waist circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Yes</td>
</tr>
<tr>
<td>Female</td>
<td>No</td>
</tr>
</tbody>
</table>

Proximal neoplasia
Compound by family history
Insulin resistance

Take Home Message #5

Lifestyle factors are major risk factors for colorectal cancer and should be addressed aggressively as early as possible

- Physical activity
- BMI
- Smoking

COLORECTAL CANCER
EARLY DETECTION/SCREENING
Colorectal Cancer Screening Tests

**Structural**
- Flexible sigmoidoscopy (FSIG)
- Optical colonoscopy (OC)
- Computed tomographic colonography (CTC)

**Fecal**
- Fecal blood test (FBT)
  - Guaiac-based occult (gFOBT; Hemoccult II)
  - High-sensitivity gFOBT; Hemoccult SENSA
  - Fecal immunochemical tests (FIT; FlexSure, HemeSelect)
- Stool DNA (sDNA)

Optical Colonoscopy – The Benchmark

<table>
<thead>
<tr>
<th>Study</th>
<th>OC vs. VC (CTC)</th>
<th>Sensitivity (≥ 10 mm)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton (JAMA, 2004)</td>
<td>100% sens.</td>
<td>OC vs. VC (CTC)</td>
<td>2.1% miss rate (≥ 10 mm)</td>
</tr>
<tr>
<td>van Rijn (AJG, 2006)</td>
<td>Tandem OC</td>
<td>Advanced neopl. 2.6% vs. 6.4%</td>
<td></td>
</tr>
<tr>
<td>Barclay (NEJM, 2006)</td>
<td>Withdrawal time &lt; 6 vs. ≥ 6 min n = 7,882</td>
<td>Perforation rates 1-3 per 1,000</td>
<td></td>
</tr>
<tr>
<td>Dominitz (Gastrointest. Endosc., 2003)</td>
<td>Complications of OC</td>
<td>1-3 per 1,000</td>
<td></td>
</tr>
</tbody>
</table>

Optical Colonoscopy & Computed Tomographic Colonography

Advanced Colorectal Neoplasia

- Adenocarcinoma
- Advanced Adenoma
  - Diameter ≥ 10 mm
Performance of Non-Invasive Screening Tests – Advanced Neoplasia

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>gFOBT</td>
<td>13%</td>
<td>93%</td>
<td>Morikawa 2005</td>
</tr>
<tr>
<td>FIT</td>
<td>20%</td>
<td>95%</td>
<td>Morikawa 2005</td>
</tr>
<tr>
<td>Fecal DNA</td>
<td>18%</td>
<td>94%</td>
<td>Imperiale 2004</td>
</tr>
<tr>
<td>CTC</td>
<td>90%</td>
<td>86%</td>
<td>Johnson 2008</td>
</tr>
</tbody>
</table>

Performance of Newer Fecal Blood Tests


<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT CRC</td>
<td>81.8%</td>
<td>96.9%</td>
</tr>
<tr>
<td>AA</td>
<td>29.5%</td>
<td>97.3%</td>
</tr>
<tr>
<td>Sensitive CRC</td>
<td>64.3%</td>
<td>90.1%</td>
</tr>
<tr>
<td>AA</td>
<td>41.3%</td>
<td>90.6%</td>
</tr>
<tr>
<td>FIT + CRC</td>
<td>64.3%</td>
<td>98.1%</td>
</tr>
<tr>
<td>AA</td>
<td>22.8%</td>
<td>98.4%</td>
</tr>
</tbody>
</table>

FIT: Fecal immunochemical test; FlexSure OBT/Hemoccult ICT
Sensitive GT: Guaiac fecal occult blood test; Hemoccult Sensa

Current Screening Recommendations


- ADENOMAS & CANCER
  - FSIG – 5 y interval or
  - Colonoscopy – 10 y or
  - DCBE – 5 y or
  - CTC – 5 y

- PRIMARILY CANCER
  - Annual gFOBT or
  - Annual FIT or
  - Stool DNA test – interval uncertain

AN ALREADY CONFUSING MESSAGE MADE MORE CONFUSING
Colorectal Cancer Screening
US Preventive Services Task Force

<table>
<thead>
<tr>
<th>TEST</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-sensitivity FBT, Hemocult SENSA or FIT</td>
<td>Annual</td>
</tr>
<tr>
<td>High-sensitivity FBT + FSIG</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 10 years</td>
</tr>
</tbody>
</table>

*For reasons not evidence-based, availability of FSIG is now very restricted in US*

DEFICIENCIES OF COLONOSCOPY
Fixable and Unfixable

Screening Colonoscopy –
Disadvantages, Deficiencies, Misuse

1. Costs
2. Complications – finite mortality
3. Subject reluctance
4. Missed and subtle lesions:
   - post-screening invasive CRC
5. The right-sided conundrum
6. Under- and overuse
Adults Aged 50 to 64 Years

Percentages Who Never Had Colonoscopy

Mitka M. JAMA 299, 622 (2008)

Non-Polypoid Colorectal Neoplasms (NP-CRN)


Prevalence of NP-CRN in screenees = 5.84%

NON-POLYPOID MORPHOLOGY ↑ CARCINOMA RISK

\[
\begin{array}{c|c|c}
\text{OR} & \text{CI} \\
\hline
\text{Overall} & 9.78 & 3.93-24.4 \\
\text{Size-adjusted} & 2.01 & 0.27-15.3 \\
\end{array}
\]

Colonoscopy and Death From Colorectal Cancer


10,292 deaths from CRC and 5 matched controls/case
7.0% of case patients and 9.8% of controls had colonoscopy

Odds Ratio (95% CI)

\[
\begin{array}{ccc}
\text{All Cancer} & \text{Right-Sided} & \text{Left-Sided} \\
& \text{Cancer} & \text{Cancer} \\
\hline
0.69 (0.63-0.74) & 0.99 (0.86-1.14) & 0.33 (0.28-0.39) \\
\end{array}
\]
Colonoscopy Follow-Up/Surveillance

Gastroenterology 130, 1872-1875 (2006)

- No Adenoma: 10 years
- Non-Advanced Adenoma: 5 years
- *Advanced Adenoma or >2 Adenomas: 3 years

*Diameter ≥ 10 mm, or villous histology or high-grade dysplasia

Surveillance Colonoscopy – Utilization


Surveillance colonoscopy within 5 years:
- Advanced adenoma: 58.4%
- > 2 Non-advanced adenomas: 57.5%
- 1 or 2 Non-advanced adenomas: 46.7%
- No adenomas: 26.5%

Substantial overuse of colonoscopy in low-risk subjects and underuse in subjects with advanced adenomas or >2 adenomas

RECOMMENDATION

Descending order of preference

- Colonoscopy
- CTC
- FIT or Hemoccult SENSA

FBT only as recommended by manufacturer
- i.e., never smear from DRE for screening
- Abandon use of traditional guaiac tests (Hemoccult II)
Take Home Message #6
Everyone should undergo periodic screening for colorectal cancer between the ages of 50 and 75 years
- Screening should be tailored to individual risk
- Individuals at increased risk should be screened by colonoscopy
- For those at average risk, CT colonography or FBT (FIT or Hemoccult SENSA) are acceptable alternatives, NOT Hemoccult II
- When available, FSIG also acceptable

COLORECTAL CANCER PREVENTION
Beyond Lifestyle Changes & Screening

REDUCING CRC MORTALITY
Triaging Risk

≤ 10% of population
CHEMOPREVENTION
A CONSIDERATION

≥ 90% of population
CHEMOPREVENTION
NOT A CONSIDERATION

Colonoscopic & Histologic Findings
- Advanced adenoma(s)
- ≥ 2 adenomas regardless of size & histology

Factors Further Increasing CRC Risk
- Family history (FDR)
- Prior CRC
- Metachrony (new adenomas at >1 surveillance colonoscopy)
- Lifestyle factors
  - BMI ≥ 30
  - Lack of physical activity
  - Smoking

Screening

Colonoscopic & Histologic Findings
- Normal examination
- ≤ 2 (<1 cm) tubular adenoma(s)
Chemoprevention – Possible Niches

- Advanced & multiple (>2) adenomas
- Genetically predisposed (family history)
- Predisposing lifestyles, e.g. BMI >30
  + inflammatory markers

Colorectal Adenoma Recurrence
A Surrogate for Colorectal Cancer

CRA Recurrence Trials (max. duration = 5 years)

Pathway to Adenoma Initiation

Adenoma Recurrence RCTs
Drugs and Micronutrients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>81 mg</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td></td>
<td>325 mg</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Ca^{2+}</td>
<td>1,200 mg</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Folic Acid</td>
<td>1 mg</td>
<td>×</td>
<td></td>
</tr>
</tbody>
</table>
RCT of Difluoromethylornithine (DFMO) + Sulindac

<table>
<thead>
<tr>
<th></th>
<th>Recurrence (%)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Adenoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>41.1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>DFMO + Sul.</td>
<td>12.3</td>
<td>0.3 (0.19-0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Advanced Ad.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>8.5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>DFMO + Sul.</td>
<td>0.7</td>
<td>0.085 (0.011-0.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Multiple Ad.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>13.2</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>DFMO + Sul.</td>
<td>0.7</td>
<td>0.055 (0.0074-0.41)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DFMO 500 mg daily
Sulindac 150 mg daily

Odds Ratios for Adenoma Recurrence by ODC Genotype and Aspirin Use

<table>
<thead>
<tr>
<th>Odds Ratio*</th>
<th>1.0 (Reference)</th>
<th>0.1 (Low-Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No aspirin</td>
<td>0.66</td>
<td>0.68</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.30-1.43</td>
<td>0.48-0.98</td>
</tr>
</tbody>
</table>
* Adjusted for age, gender and number of colonoscopies

Take Home Message #7
For a minor proportion of the population, chemoprevention may be a consideration, though not yet accepted as part of usual care
• Low-dose aspirin and calcium supplements
• DFMO ± NSAID shows considerable promise
• Tailored
• Patient categories for consideration include
  - Prior colorectal cancer
  - Advanced & multiple (>2) adenomas
  - Genetically predisposed (family history)
  - Predisposing lifestyles, e.g. BMI >30
  + Inflammatory markers (speculative)
Preventing Colorectal Cancer

1. Cancer health disparities must be eliminated
2. Prior CRC or advanced/multiple adenomas confer ↑ risk
3. Be informed of family history (FDR) of CRC
4. Patients with ulcerative or Crohn’s colitis at ↑ risk
5. Lifestyle factors (obesity/BMI, lack of physical activity) are major risk factors for CRC
6. Everyone between ages of 50 and 75 years should undergo periodic screening
   a. Colonoscopy for those at increased risk
   b. CTC or FBT (FIT or Hemoccult SENSA) acceptable for those at average risk. If available, FSIG acceptable
7. Chemoprevention a viable consideration for a minority of the population at increased risk for CRC