Colorectal Cancer: Early Detection and Prevention

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Professor of Medicine & Epidemiology
University of Pittsburgh, Pittsburgh, PA
U.S. Colorectal Cancer - Epidemiology

- 2\textsuperscript{nd} leading cause of CA mortality in U.S.
- 3\textsuperscript{rd} most common cancer
- > 136,000 new cases in 2014
- > 50,000 deaths in 2014
Lifetime Risk of CRC (%)

<table>
<thead>
<tr>
<th></th>
<th>LR Diagnosis</th>
<th>LR Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>5.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Women</td>
<td>4.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Siegel R. CA Cancer J Clin 2014:64:104
Colorectal Cancer Incidence by Age

Age 50 →

Rate per 100,000

Age at diagnosis

0  10  20  30  40  50  60  70  80  90  100

Male and female
Male
Female
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'84 - '02</td>
<td>-1.9</td>
<td>-1.8</td>
</tr>
<tr>
<td>'01 – ‘10</td>
<td>-3.0</td>
<td>-3.0</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'95 - '98</td>
<td>1.1</td>
<td>1.9</td>
</tr>
<tr>
<td>'98 - ’04</td>
<td>-2.8</td>
<td>-2.4</td>
</tr>
<tr>
<td>'01 – ‘10</td>
<td>-3.8</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

Espey, Cancer 2007;Oct 15
Siegel R. CA Cancer J Clin 2014:64:104
U.S. CRC Incidence and Mortality Trends

Siegel R. CA Cancer J Clin 2014:64:104
Endoscopic Screening
The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

• Sponsored by NCI
• 10 U.S. clinical centers
• Randomized: Screening vs. Usual Care
• Screening began in 1993, concluded in 2001
• Followed mean 11 yr

Schoen, NEJM 2012;366:2345
Protocol

Randomized
N=154,900

Intervention
N=77,445

Initial FSG Screen

Second Screen at yr 3 or 5

Usual Care
N=77,455

All analyzed and included
# Overall CRC Incidence

<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td># Cases</td>
<td>1287</td>
<td>1012</td>
</tr>
<tr>
<td>Rate/10K PY</td>
<td>15.2</td>
<td>11.9</td>
</tr>
<tr>
<td>RR</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(.72-.85)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

**Mean F/U 11.2 yr; Median 11.9 yr**

21% decrease in incidence

275 fewer cases
Overall Colorectal Cancer Incidence by Year

### Cumulative Cases

<table>
<thead>
<tr>
<th>Years Since Randomization</th>
<th>Intervention Cancers</th>
<th>Usual Care Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>242</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>347</td>
<td>344</td>
</tr>
<tr>
<td></td>
<td>487</td>
<td>564</td>
</tr>
<tr>
<td></td>
<td>659</td>
<td>790</td>
</tr>
<tr>
<td></td>
<td>797</td>
<td>998</td>
</tr>
<tr>
<td></td>
<td>927</td>
<td>1169</td>
</tr>
<tr>
<td></td>
<td>1012</td>
<td>1287</td>
</tr>
</tbody>
</table>

### Person-years

<table>
<thead>
<tr>
<th>Years Since Randomization</th>
<th>Intervention Person-years</th>
<th>Usual Care Person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>76520</td>
<td>76592</td>
</tr>
<tr>
<td></td>
<td>227007</td>
<td>227438</td>
</tr>
<tr>
<td></td>
<td>373895</td>
<td>374467</td>
</tr>
<tr>
<td></td>
<td>516773</td>
<td>517055</td>
</tr>
<tr>
<td></td>
<td>654740</td>
<td>654447</td>
</tr>
<tr>
<td></td>
<td>772625</td>
<td>771744</td>
</tr>
<tr>
<td></td>
<td>848403</td>
<td>847103</td>
</tr>
</tbody>
</table>
Overall: Mortality to CRC

<table>
<thead>
<tr>
<th>Usual Care</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td># Deaths</td>
<td># Deaths</td>
</tr>
<tr>
<td>341</td>
<td>252</td>
</tr>
<tr>
<td>Rate/10K PY</td>
<td>Rate/10K PY</td>
</tr>
<tr>
<td>3.9</td>
<td>2.9</td>
</tr>
</tbody>
</table>

RR: 0.74 (0.63-0.87)  P < .001

26% decrease in mortality
89 fewer deaths
## Randomized Trials of Flexible Sigmoidoscopy: Effect on Incidence and Mortality

<table>
<thead>
<tr>
<th></th>
<th>ITT Overall Reduction</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK</strong></td>
<td></td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td><strong>Italy</strong></td>
<td></td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td><strong>PLCO (U.S.)</strong></td>
<td></td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td><strong>Norway</strong></td>
<td></td>
<td>20</td>
<td>27</td>
</tr>
</tbody>
</table>

**Distal Colon**

<table>
<thead>
<tr>
<th></th>
<th>ITT Overall Reduction</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK</strong></td>
<td></td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td><strong>Italy</strong></td>
<td></td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td><strong>PLCO (U.S.)</strong></td>
<td></td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td><strong>Norway</strong></td>
<td></td>
<td>24</td>
<td>31</td>
</tr>
</tbody>
</table>

*Pink = Not significant*
If half is good, whole must be....
Colonoscopy: Is it Effective in the Proximal Colon?
Observational Studies of Colonoscopy

- Uncertain effectiveness in reducing proximal CRC mortality
- Less protection against proximal than distal cancer

Baxter N, Annals 2009;150:1
Singh, Gastro 2010;139:1128
What About The Proximal Colon – Why is It More Difficult To Protect?
Why Right ≠ Left?

1. Biology
   - Molecular (CIMP, MSI)
   - Progression – Polyp recurrence more common in right colon

2. Operator
   - Missed Lesions: Flat
   - Serrated Adenomas: Mucin Covered
   - Bowel Prep
   - Incomplete CS
# Ongoing Randomized Colonoscopy Screening Effectiveness Trials

<table>
<thead>
<tr>
<th>Started 2012</th>
<th>Started 2009</th>
<th>Started 2009</th>
<th>Started 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONFIRM</strong></td>
<td><strong>NordICC</strong></td>
<td><strong>COLONPREV</strong></td>
<td><strong>SCREESCO</strong></td>
</tr>
<tr>
<td>50,000 participants</td>
<td>95,000 participants</td>
<td>57,000 participants</td>
<td>200,000 participants</td>
</tr>
<tr>
<td>USA (VA)</td>
<td>Poland, Norway, Netherlands, Sweden</td>
<td>Spain</td>
<td>Sweden</td>
</tr>
</tbody>
</table>

**Randomization**

- **CONFIRM**
  - Annual FIT
  - FIT
  - FIT
  - FIT
  - FIT
  - FIT
  - 10 year Colorectal Cancer Mortality

- **NordICC**
  - No screening
  - FIT
  - FIT
  - FIT
  - 15 year Colorectal Cancer Mortality

- **COLONPREV**
  - Biennial FIT
  - FIT
  - FIT
  - 10 year Colorectal Cancer Mortality

- **SCREESCO**
  - No screening
  - Biennial FIT
  - FIT
  - FIT
  - 15 year Colorectal Cancer Mortality

Robertson DJ et al. Gut 2015;64:982-990
If We Have Such Good Screening Tests, Do We Need A Biomarker?

- Even if you have a great test, still have to get subjects to comply. A biomarker than can stimulate evaluation of the population at risk is worthwhile.

- In colon, testing is effective, but trying: stool tests, endoscopic testing.

- BLOOD TEST is next frontier.
U.S. CRC Screening Test Use

- Up to date with recommended screening:
  54% in 2002 → 65% in 2010
- Disparities in utilization

MMWR 2012;62:881
FOBT (past 1 yr) or Endoscopy (previous 10 yr): BRFSS

- OK: 53%
- MA: 74%
- AK: 56%
- MA: 76%
### Disparity in Screening for CRC

<table>
<thead>
<tr>
<th>Factor</th>
<th>Percentage Up to Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>53.1</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>66.4</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; HS</td>
<td>48.3</td>
</tr>
<tr>
<td>College Grad</td>
<td>73.5</td>
</tr>
<tr>
<td><strong>Annual Income</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 15k</td>
<td>49.5</td>
</tr>
<tr>
<td>&gt; 75k</td>
<td>74.0</td>
</tr>
<tr>
<td><strong>Insurance</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>36.9</td>
</tr>
<tr>
<td>Yes</td>
<td>68.9</td>
</tr>
</tbody>
</table>

MMWR 2012;62:881
Distribution of Colonoscopy Findings (N=9,989)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Valid Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>65</td>
</tr>
<tr>
<td>Advanced Adenoma</td>
<td>757</td>
</tr>
<tr>
<td>Non-advanced adenoma</td>
<td>2,893</td>
</tr>
<tr>
<td>Negative</td>
<td>6,274</td>
</tr>
</tbody>
</table>

Do We Need A Biomarker?

• A biomarker could increase utilization
• Testing we have, though effective, is inefficient and expensive
EDRN: The Search for Biomarkers for CRC
Conducting a 6 - 12,000 patient study evaluating stool markers, serum markers in relation to colonoscopy outcomes
ct-DNA for Early Detection and Monitoring of CRC
ct-DNA: Circulating Tumor DNA

- Small fragments of nucleic acid (160-180bp) that originate from apoptotic cell turnover
- Mutational profile corresponds to that in tumor tissue
- Half life <1.5 hours
Released DNA as a Cancer Biomarker

Circulating Tumor DNA (ctDNA)

Stool Tumor DNA (sDNA)

Risk Assessment  Screening  Diagnosis/Prognosis  Monitoring  Response Prediction  Monitoring Resistance
Experimental Design

- **Tumor** → DNA → Direct Sequencing
- **Plasma** → SafeSeqS
  - WT → UID Assignment → Mutant
  - Amplification → Redundant Sequencing
  - Fluorescence Intensity (Cy5)

**Mutation**
e.g. APC 1338 C > T

**Total DNA Concentration**
e.g. 11,500 DNA fragments per sample

**% Mutations**
e.g. 0.27%
Safe-SeqS

Method for detection and quantification of rare mutations

Kinde I et al. PNAS 108:9530-9535, 201
Essential elements of Safe-SeqS

Sequencing or Replication Error

This strategy can decrease error rates by 70-fold
ctDNA in Advanced Cancers

![Bar chart showing the frequency of cases with detectable ctDNA for various cancers.](chart.png)
ctDNA in Advanced CRC
Localized disease: 73%
ctDNA as a Marker of Therapeutic Response in Stage IV CRC

- N=53, serial blood collection, CT week 8-10
- RECIST: image-based Response Evaluation Criteria in Solid Tumors
- Explore ctDNA as a marker of treatment response

ctDNA correlates with baseline RECIST SLD (sum of longest tumor diameters). ctDNA decreases with chemoRx, CEA shows no change.
Fold change in ctDNA correlates with change in RECIST: ctDNA response mirrors imaging response.

≥ 10 fold ctDNA reduction predicts progression free survival.
Conclusions

- ≥10 fold ctDNA reduction pre-cycle 2 (@14-21 days) predicts progression free survival (14.7 vs. 8.1 months)
Application

- Could use ct-DNA to prognosticate
- Could use ct-DNA to try a different chemoRx
### ctDNA After Surgery in Stage II CRC: Predicts Disease Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>No recurrence</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op ctDNA - positive</td>
<td>7</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Post-op ctDNA - negative</td>
<td>7</td>
<td>96</td>
<td>103</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>97</td>
<td>112</td>
</tr>
</tbody>
</table>

- Fisher’s Exact $P < 0.0001$
- RR = 11.44
  
  (95% CI 5.16 – 25.37)

Positive predictive value = 77.8%

Negative predictive value = 93.2%
Post-op ctDNA, time-to-recurrence and CRC-specific survival

**Time to Recurrence**

- Post-op ctDNA negative
- Post-op ctDNA positive

HR = 25.73
P < 0.0001

**CRC-specific Survival**

- Post-op ctDNA negative
- Post-op ctDNA positive

P < 0.0001
Time-to-recurrence according to post-op ctDNA results for patients with T3 and T4 tumor

HR = 40.42, P < 0.0001
HR = 12.55, P < 0.0001
Conclusions

- ctDNA is a marker for recurrence in patients with stage II CRC
- ctDNA findings discriminate within clinicopathologic subgroups
Could use ct-DNA to aid in decision of who should get chemoRx in stage II CRC
Immuno-Prevention

Immunize people at high risk for cancer when the immune system is still powerful and effective

Immunotherapy in a Preventive Mode: Immune Interception

Kimura. Ca Prev Resch 2013;6:18
Dhodapkar. Ca Prev Resch 2013;6
Normal MUC1

Abnormal MUC1

1 repeat = 20 a.a.

HGVTSAPDTRPAPGSTAPPA

O-LINKED OLIGOSACCHARIDES ON THE TANDEM REPEATS

PROTEOLYTIC SPLICE SITE

TRANSMEMBRANE DOMAIN (28 a.a.)

CYTOPLASMIC TAIL (72 a.a.)
Basolateral side

Apical (luminal) side

Polyp or Tumor

Hypoglycosylated MUC1 on entire surface

Protein backbones, which on normal tissue are concealed by glycosylation are exposed to immune system.
Abnormal Mucins Exposed to Systemic Circulation

NORMAL

Mucins

Basement membrane

Blood vessel

CANCER/ADENOMA

Altered glycans

Secretion of mucins into the bloodstream
Vaccine Prevention Trial Against Tumor Associated Antigen

Subjects with advanced adenomas who are at higher risk to develop colorectal cancer: Vaccinate them against tumor associated MUC1 antigen

Ratio range among Responders: 2.2 – 36.3

Peak response week 12, post 3rd injection
Booster response at week 54
Randomized, Double-Blind, Placebo-Controlled Trial of MUC1 Vaccine in Patients with Newly Diagnosed Advanced Adenomas

• In Conjunction with the Mayo Cancer Prevention Network (CPN) and the NCI Division of Cancer Prevention

• 7 centers
Trial Progress

Date: June 10, 2015

Accrual Update for MAY2013-01-01, “Randomized, Double-Blind, Placebo-Controlled Trial of MUC1 Vaccine in Patients with Newly Diagnosed Advanced Adenomas”

<table>
<thead>
<tr>
<th>Site</th>
<th>Pre-Registered</th>
<th>Randomized</th>
<th>“Next Tasks”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic in Rochester</td>
<td>12</td>
<td>10</td>
<td>Identifying potential participants using pathology report.</td>
</tr>
<tr>
<td>University of Pittsburgh</td>
<td>21</td>
<td>20</td>
<td>Randomized 4 participants the month of May by reviewing pathology reports.</td>
</tr>
<tr>
<td>University of Puerto Rico</td>
<td>12</td>
<td>11</td>
<td>Jessica is actively screening potential participants in clinic.</td>
</tr>
<tr>
<td>Massachusetts General Hospital</td>
<td>2</td>
<td>1</td>
<td>One appointment scheduled for consent/screening.</td>
</tr>
<tr>
<td>Thomas Jefferson University</td>
<td>8</td>
<td>4</td>
<td>No report provided.</td>
</tr>
<tr>
<td>Kansas City VA Medical Center</td>
<td>4</td>
<td>4</td>
<td>Welcome Andrew Price – he randomized a patient his first week! Way to go!</td>
</tr>
<tr>
<td>Fox Chase Cancer Center</td>
<td></td>
<td></td>
<td>Eileen is reviewing path reports daily to identify potential participants.</td>
</tr>
</tbody>
</table>

| Totals                            | 59             | 50         |

Current Status: All sites are actively recruiting study participants.

Reminder: Please submit VSA4 of the protocol to your local IRBs as soon as possible and forward your approval to the CPN Operations office. Submissions should take place within 30 days of receipt of the amendment documents.

Next Study Coordinator Call is Thursday June 18th at 10 a.m. EDT; 9 a.m. CDT. Please let us know if you have any discussion items for the agenda.

Enrollment - 55 Halfway There!
Enrollment = 50 (June 10, 2015)
First participant (July 10, 2014)
Optimizing CRC Screening

- Access for all at risk
- Develop new more accessible means to increase screening utilization
- Develop new methods for prevention such as vaccines or personalized medicine
Fold change in ctDNA correlates with change in RECIST: ctDNA response mirrors imaging response.

≥ 10 fold ctDNA reduction predicts progression free survival.

Fold change in ctDNA is best predictor of reduction in tumor burden by imaging.

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