Colon Cancer in the young

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November, 2019
function MM_swapImgRestore() { //v3.0
var i,x,a=document.MM_sr; for(i=0;a&&i<a.length&&x=a[i]&&x.oSrc;i++) x.src=x.oSrc;
function MM_preloadImages() { //v3.0
var d=document; if(d.images){ if(!d.MM_p)d.MM_p=new Array();var i,j=d.MM_p.length,a=MM_preloadImages.arguments; for(i=0;a&&(j=i)++;i++) if (a[j].indexOf("#")!=0){d.MM_p[j]=new Image; d.MM_p[j].src=a[i];}}
function MM_findObj(n, d) { //v4.01
var p,i,x; if(!d) d=document; if((p=n.indexOf("?"))>0&&parent.frames.length){d=parent.frames[n.substring(p+1)].document; n=n.substring(0,p);}
if(!x)d[n]; if(d.all)x=d.all[n]; for(i=0;!x&&i<d.forms.length;i++) x=d.forms[i][n];
for(i=0;!x&&d.layers&&!i<d.layers.length;i++) x=MM_findObj(n,d.layers[i].document);
if(!x) if(d.getElementById)n=d.getElementById(n); return x;
function MM_swapImage() { //v3.0
var i,j=0,x,a=MM_swapImage.arguments; document.MM_sr=new Array; for(i=0;i<(a.length-2);i++)
if ((x=MM_findObj(a[i]))!=null){document.MM_sr[i]=x; if(!x.oSrc)x.oSrc=x.src; x.src=a[i+2];}
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Conflicts of Interest: Translated

Ironwood Pharmaceuticals: PI Study C3718-301
Allergan Pharmaceuticals: Sub-I Study 3150-201
Allergan Pharmaceuticals: Sub-I Study 3151-201
**Typical Conflicts of Interest Statement, Properly Revealed:**

<table>
<thead>
<tr>
<th>Engagement</th>
<th>% of professional compensation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ironwood Pharma</td>
<td>&lt; .04%</td>
</tr>
<tr>
<td>Allergan Pharma</td>
<td>&lt; .04%</td>
</tr>
</tbody>
</table>
Ideal Conflict of Interest Statement:

Engagement: % of professional compensation:

Southwest Gastroenterology 100%

Nature of potential bias: Presenter does clinical care of gastroenterology patients including colonoscopy.
Risk factors for Colon Cancer

Age
Inherited Genetic syndrome
Inflammatory Bowel Disease involving the colon
Abdominal or Pelvic irradiation
Lifestyle and other “choices”
  Diet (red meat, processed meats vs fiber, veges)
  Obesity
  Diabetes
  Physical Activity
  Alcohol
  Smoking
Estrogen replacement
NSAID/ASA use
Epidemiology of Colon Cancer

Colorectal cancer incidence: SEER data, 2011 to 2015

Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society

The American Cancer Society has recently recommended decreasing the screening age to 45 y/o: Wolf et al. Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update from the American Cancer Society. CA: A Cancer Journal for Clinicians 2018; 68: 250 (July/August issue)

1 in 10 new colon cancers will be at age < 50

The incidence of colon cancer in younger patients is projected to double by 2030
### Colon Cancer Diagnoses at Southwest Gastroenterology

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Total colon cancers (214)</td>
<td>3</td>
<td>30</td>
<td>26</td>
<td>22</td>
<td>0</td>
<td>16</td>
<td>31</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>50+</td>
<td>3</td>
<td>25</td>
<td>24</td>
<td>21</td>
<td>16</td>
<td>24</td>
<td>33</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Average age</td>
<td>67</td>
<td>63</td>
<td>64</td>
<td>68</td>
<td>66</td>
<td>63</td>
<td>65</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

Thus $22/214 = \approx 10\%$ of new diagnoses are in pts $< 50$ y/o

The data set is too small to see a trend...
Obesity is on the rise
Inflammatory Bowel disease is on the rise
Diets are evolving (not necessarily in a positive way)
Cohort effect of unclear nature

The identified risk factors do not explain the changing epidemiology.
Each 5 unit increase in BMI increased Colon Ca risk by 13-18%!

Diabetes is associated with an increased risk of up to 38% (20% for rectal cancer)

Regular physical activity is associated with a 24-31% decrease in risk.

(Increased) relative risks are in the range of 1.3-2.0
In a case/control observational study, an odds ratio for association can be calculated, but relative risk can only be estimated.

In a cohort study, relative risk can be calculated. The observed relative risks for several possible PPI side effects are nearly always <2 and often < 1.6. In this low range, confounding factors may be responsible for “risks” of this magnitude.

Causation is even tougher to prove: dose response and duration effects are inconsistently present.
What happens to Younger People when they get Colon cancer?

More often present with advanced disease: Symptomatic young patients wait 6 months before seeking care!

More often have left sided disease, particularly rectal. But for a given stage, survival is better than older folks.

18% of patients < 50 y/o have a germline mutation
35% of patients < 35 y/o have a germline mutation
<table>
<thead>
<tr>
<th>AJCC stage</th>
<th>Survival rate (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger (20-40 y) (n=1196)</td>
<td>Older (60-80 y) (n=35,837)</td>
<td>$P$ value</td>
</tr>
<tr>
<td>All</td>
<td>61.5</td>
<td>64.9</td>
<td>.02</td>
</tr>
<tr>
<td>I</td>
<td>93.3</td>
<td>94.9</td>
<td>NS</td>
</tr>
<tr>
<td>II</td>
<td>88.6</td>
<td>82.7</td>
<td>.01</td>
</tr>
<tr>
<td>III</td>
<td>58.9</td>
<td>57.2</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>18.1</td>
<td>6.2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
None of the current screening strategies have been properly studied in younger age groups.

Participation in screening strategies is as important as test characteristics and cost for long term outcomes.
## Symptoms associated with colorectal cancer

<table>
<thead>
<tr>
<th>Symptom</th>
<th>DOR* (95% CI)*</th>
<th>AUC †</th>
<th>Sensitivity (95% CI)</th>
<th>1−specificity (95% CI)</th>
<th>LR+ (95% CI)</th>
<th>LR− (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding Δ</td>
<td>2.6 (1.9-3.6)</td>
<td>0.66</td>
<td>0.46 (0.38-0.52)</td>
<td>0.25 (0.19-0.31)</td>
<td>1.9 (1.5-2.3)</td>
<td>0.7 (0.5-0.8)</td>
</tr>
<tr>
<td>Blood mixed with stool</td>
<td>3.1 (2.0-4.8)</td>
<td>0.68</td>
<td>0.48 (0.40-0.65)</td>
<td>0.24 (0.13-0.40)</td>
<td>2.1 (1.5-2.8)</td>
<td>0.7 (0.5-0.9)</td>
</tr>
<tr>
<td>Blood: dark red</td>
<td>3.9 (1.7-9.2)</td>
<td>0.71</td>
<td>0.29 (0.09-0.67)</td>
<td>0.10 (0.03-0.28)</td>
<td>3.1 (1.6-6.0)</td>
<td>0.8 (0.5-1.1)</td>
</tr>
<tr>
<td>Change in bowel habit</td>
<td>1.5 (0.8-2.8)</td>
<td>0.57</td>
<td>0.32 (0.21-0.46)</td>
<td>0.24 (0.15-0.35)</td>
<td>1.4 (0.9-2.1)</td>
<td>0.9 (0.7-1.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.1 (0.8-1.5)</td>
<td>0.52</td>
<td>0.12 (0.08-0.18)</td>
<td>0.11 (0.07-0.10)</td>
<td>1.1 (0.8-1.5)</td>
<td>1.0 (1.0-1.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.9 (0.4-1.7)</td>
<td>0.47</td>
<td>0.15 (0.07-0.28)</td>
<td>0.17 (0.09-0.29)</td>
<td>0.9 (0.5-1.6)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.7 (0.5-1.1)</td>
<td>0.45</td>
<td>0.19 (0.13-0.28)</td>
<td>0.24 (0.17-0.33)</td>
<td>0.8 (0.6-1.1)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2.9 (1.6-5.0)</td>
<td>0.57</td>
<td>0.20 (0.12-0.31)</td>
<td>0.08 (0.05-0.13)</td>
<td>2.3 (1.5-4.0)</td>
<td>0.6 (0.5-1.0)</td>
</tr>
</tbody>
</table>

LR+: the likelihood ratio of having colorectal cancer in the presence of the symptom; LR−: the likelihood ratio of having colorectal cancer in the absence of the symptom.

* DOR: diagnostic odds ratio. No association between symptom and cancer if DOR = 1.
† AUC: Area Under the receiver operating characteristic Curve. No association between symptom and cancer if AUC = 0.5.
Δ Bleeding of any type.

About $15,000 per QUALY

Compares favorably with a “standard” threshold of $50 – 100K/QUALY

But the best screening strategy is the one that is acceptable to the individual patient – as any screening modality is much better than no screening.
Test for Colon Cancer Screening.

Estimated sensitivity, specificity, and cancer-specific deaths averted for each colorectal cancer screening strategy:

- Sensitivity for adenomas ≤5 mm
- Sensitivity for adenomas 6 to 9 mm
- Sensitivity for adenomas ≥10 mm
- Sensitivity for colorectal cancer
- Specificity

<table>
<thead>
<tr>
<th>Screening Strategy</th>
<th>22 to 24</th>
<th>20 to 23</th>
<th>16 to 24</th>
<th>16 to 21</th>
<th>20 to 23</th>
<th>21 to 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL</td>
<td>85</td>
<td>95</td>
<td>88</td>
<td>75</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>FIT</td>
<td>85</td>
<td>95</td>
<td>88</td>
<td>75</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>CTC</td>
<td>72.0</td>
<td>75</td>
<td>84</td>
<td>88</td>
<td>75</td>
<td>82.5</td>
</tr>
<tr>
<td>SIG*</td>
<td>84</td>
<td>84</td>
<td>88</td>
<td>87</td>
<td>75</td>
<td>12.4</td>
</tr>
<tr>
<td>gFOBT</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>42.4</td>
<td>42.4</td>
</tr>
<tr>
<td>FIT-DNA</td>
<td>92.3</td>
<td>92.3</td>
<td>92.3</td>
<td>95.0</td>
<td>92.3</td>
<td>92.3</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, and cancer-specific deaths averted for each screening strategy:

- COL: colonoscopy
- FIT: fecal immunochemical test
- CTC: computed tomography colonography
- SIG*: sigmoidoscopy
- gFOBT: guaiac-based fecal occult blood test
- FIT-DNA: multiaffected stool DNA test

* Assumes screening from ages 50 to 75 years, including 100% adherence, complete follow-up without delay, and appropriate surveillance. Ranges reflect results from 3 models. Stool tests assume yearly testing, sigmoidoscopy assumes testing every 5 years, CTC assumes testing every 5 years, colonoscopy assumes testing every 10 years.

Data from:
Current ACP Guidance:
Qaseem et al. Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A guidance statement from the ACP. Ann Int Med 2019;171:643
11/5/2019

Screen in average risk adults 50-75 y/o

FIT or gFOBT q 2 yrs OR colonoscopy q 10 yrs OR Flex sig q 10 plus FIT q2yrs

Stop at age 75 or with life expectancy < 10 yrs
What we really need to make good decisions about (any) screening:

1) A good way to estimate general prognosis

2) A good way to estimate risk of disease
Can we be more selective about screening?

http://magicproject.org/19022dist
### About you

**Clinical information**

- Do you have a family history of ...
  - Women only: have you had any of these cancers?
  - Men only: have you had any of these cancers? (These cancers did not pass our statistical test for significance for women.)

- Do you currently have... Leave blank if unknown
- Body mass index
- Calculate risk over years.

<table>
<thead>
<tr>
<th>Age (25-84):</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td>Male</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td>White or not stated</td>
</tr>
<tr>
<td>UK postcode:</td>
<td>leave blank if unknown</td>
</tr>
<tr>
<td>Postcode:</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical information

- Smoking status:
- Alcohol status:
- Do you have a family history of ...
  - gastro-intestinal cancer?
  - Women only: have you had any of these cancers?
    - breast cancer?
    - uterine cancer?
    - ovarian cancer?
    - cervical cancer?
  - Men only: have you had any of these cancers? (These cancers did not pass our statistical test for significance for women.)
    - oral cancer?
    - lung cancer?
    - cancer of the blood?

- Do you currently have...
- Diabetes:
- ulcerative colitis?
- colonic polyps?
- Leave blank if unknown

<table>
<thead>
<tr>
<th>Height (cm):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg):</td>
<td></td>
</tr>
</tbody>
</table>

Calculate risk over **15** years.

<table>
<thead>
<tr>
<th>Calculate risk over 15 years:</th>
<th>Calculate risk</th>
</tr>
</thead>
</table>
Hypothesis: If we could be more selective, would the uptake of CRC screening by better defined at risk population be better than the current approx. 2/3?

Complex algorithms are not how most folks make decisions!
What about Cologuard?

Sensitivity of 84-97% (median 92%), specificity 84%

Heavily advertized

Numerous publications, but: All original data generated by the manufacturer!
This is a hybrid test: FIT plus abnormal DNA fragments – with no ability to learn which component is “positive”

What to do with a patient with positive Cologuard and negative colonoscopy (which will happen half the time):

a) nothing – Cotter et al. Cancer Epi Biomark Prev 2007: no increase risk in 1000 patients over 4 years

b) “more aggressive short-term surveillance”: ACP Guidance 2019
Get a good family history (review every 3 years)
Take colonic symptoms seriously in younger patients
Consider engaging in screening at age 45 – perhaps most importantly in African Americans
Encourage healthy lifestyle
Colon Cancer in the young

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