How to Screen a patient with a Family History of Adenoma(s)

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CDDW
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Disclosures 2016

• Scientific advisory board
  – MOTUS-GI
CRC Mortality Trends

CA Cancer J Clin 2014; 64: 104-117
Incidence Trends by Age

0-49 years

10% of CRC

50-64 years

65+ years

Rate per 100,000 people

Year of diagnosis

CA Cancer Clin 2014; 64: 104-117
CRC Incidence < age 54 years

Colon

20-29

30-39

40-49

50-54

Rectum

Siegel; JNCI 2017; 109
CRC <54 years
Familial Risk and Age of CRC

Figure 1. Cumulative Incidence of Colorectal Cancer According to Age and the Presence or Absence of a Family History of the Disease.

Fuchs; NEJM 1994; 331: 1669-74
Risk Factors for CRC

**Family History**: 15-20%

**HNPCC**: 3%

**FAP**: 1%

**IBD - Colitis**: 1%

**Sporadic/Average Risk**: 75%

**Simple Questions:**

Do you have a 1st degree relative with colon cancer?

If so, did the relative have cancer before age 50 yrs?
Questions posed

- Does FHX of adenoma change screening approach?
- Does age of patient change approach?
- What type of screening – FIT or colonoscopy?
The questions behind the questions

• Is lifetime risk of CRC increased in individuals with a family history of CRC?
  – If index family member < 60 yrs
  – If index family member > 60 yrs
FDR with CRC – What we know

<table>
<thead>
<tr>
<th>Family History Category</th>
<th>Pooled Risk Measure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 FDR</td>
<td>2.24 (2.06-2.43)</td>
</tr>
<tr>
<td>1 FDR &lt;50</td>
<td>3.55 (1.84-6.83)</td>
</tr>
<tr>
<td>1 FDR 45-59 years</td>
<td>2.25 (1.85-2.72)</td>
</tr>
<tr>
<td>1 FDR &gt;60</td>
<td>1.83 (1.347-2.25)</td>
</tr>
<tr>
<td>1 FDR &gt;70</td>
<td>1.97 (1.86-2.08)</td>
</tr>
<tr>
<td>≥2 FDRs</td>
<td>3.97 (2.60-6.06)</td>
</tr>
</tbody>
</table>

Lowry et al; Cancer 2016; 122:2633-45
FHx of CRC

- Question posed: does age of index case make a difference in CRC risk in family?

<table>
<thead>
<tr>
<th>Age of Index Case</th>
<th>HR FDR</th>
<th>HR FDR &lt;50</th>
<th>HR FDR &gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>2.53 (1.7-3.79)</td>
<td>2.28 (1.86-2.80)</td>
<td>1.81 (1.71-1.92)</td>
</tr>
<tr>
<td>40-49</td>
<td>2.26</td>
<td>2.93</td>
<td>2.03</td>
</tr>
<tr>
<td>50-59</td>
<td>2.35</td>
<td>2.91</td>
<td>2.29</td>
</tr>
<tr>
<td>60-69</td>
<td>1.85</td>
<td>2.09</td>
<td>1.82</td>
</tr>
<tr>
<td>70-79</td>
<td>1.69</td>
<td>2.19</td>
<td>1.67</td>
</tr>
<tr>
<td>&gt;79</td>
<td>1.76</td>
<td>1.61</td>
<td>1.76</td>
</tr>
</tbody>
</table>

Younger Index Case = Younger age of onset

Samadder et al; CGH 2015; 13: 2305-11
**FDR with CRC: # of FDRs**

<table>
<thead>
<tr>
<th>No. of affected FDRs</th>
<th>No. of probands</th>
<th>FRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2,232,396</td>
<td>0.89 (0.87–0.91)</td>
</tr>
<tr>
<td>1</td>
<td>87,089</td>
<td>1.91 (1.82–2.00)</td>
</tr>
<tr>
<td>≥1</td>
<td>94,931</td>
<td>2.05 (1.96–2.14)</td>
</tr>
<tr>
<td>2</td>
<td>6,966</td>
<td>3.01 (2.66–3.38)</td>
</tr>
<tr>
<td>3</td>
<td>762</td>
<td>4.43 (3.24–5.90)</td>
</tr>
<tr>
<td>4</td>
<td>92</td>
<td>7.74 (3.71–14.24)</td>
</tr>
<tr>
<td>≥5</td>
<td>22</td>
<td>19.86 (7.29–43.24)</td>
</tr>
</tbody>
</table>

*Table 1. Selected Familial Relative Risk (FRR) Estimates for Probands Considering Only First-Degree Relative (FDR) Family History*

*Taylor 2010*
FHX of CRC

• Question posed: do asymptomatic family members of patients with CRC have increased risk of CRC and advanced neoplasia?

• Colonoscopy: 3804 index cases with CRC

<table>
<thead>
<tr>
<th>Risk of CRC</th>
<th>Hazard Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDRs</strong></td>
<td></td>
</tr>
<tr>
<td>FDR &lt;60</td>
<td>1.79 (1.59-2.03)</td>
</tr>
<tr>
<td>FDR &gt;60</td>
<td>2.11 (1.70-2.63)</td>
</tr>
<tr>
<td></td>
<td>1.77 (1.58-1.99)</td>
</tr>
<tr>
<td><strong>SDRs</strong></td>
<td>1.32 (1.19-1.47)</td>
</tr>
<tr>
<td><strong>Cousins</strong></td>
<td>1.15 (1.07-1.25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of Adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adenoma</td>
</tr>
<tr>
<td>Adenoma with villous histology</td>
</tr>
</tbody>
</table>

Samadder et al; Gastroenterol 2014; 147: 814-21
FHX of CRC

• Question posed: do asymptomatic siblings of patients with CRC have increased risk of advanced neoplasia?

• Colonoscopy
  – 374 Siblings (36% < 50 yrs) with CRC FDR
  – Age: 52.7 yrs vs controls with no FHX
  – Prevalence of Advanced Neoplasia: 7.5% (in FDRs) vs 2.9% (in controls)
  – 6 cancers

• Suggests high-yield for screening at young age

Ng et al; Gastroenterol 2013
FHX of CRC

• Questions posed:
  – What proportion of colonoscopy in USA is performed for FHX of CRC or adenoma?
  – Do patients who have colonoscopy performed for this reason have higher likelihood of advanced neoplasia?

• CORI database
  – 70+ practices in USA in diverse settings
Proportion of all colonoscopies

Lieberman et al; GIE 2014; 80: 133-43
Women polyps >9mm

Lieberman et al; GIE 2014; 80: 133-43
Men polyps >9mm

Evidence suggests:
higher risk of advanced adenomas
at age <54 with +FHx

Lieberman et al; GIE 2014; 80: 133-43
**FHX of CRC**

- Question posed: what is the effect of FHX of CRC on CRC incidence AFTER age 55 years (when risk of early onset CRC has passed)?

<table>
<thead>
<tr>
<th>Index FHX</th>
<th>HR for CRC incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No FHX</td>
<td>1.00</td>
</tr>
<tr>
<td>≥2 FDRs</td>
<td>2.04 (1.44-2.86)</td>
</tr>
<tr>
<td>1 FDR &lt;60</td>
<td>1.27 (0.97-1.63)</td>
</tr>
<tr>
<td>1 FDR 60-70</td>
<td>1.33 (1.06-1.62)</td>
</tr>
<tr>
<td>1 FDR &gt; 70</td>
<td>1.14 (0.93-1.45)</td>
</tr>
</tbody>
</table>

Schoen et al; PLCO; Gastroenterol 2015; 149: 1438-45
FDR with CRC: What we do NOT know

• Does early screening reduce CRC incidence/mortality
  – It may if cancer precursors and detected and removed (NPS)

• Is one form of screening necessarily better than another?
  – If aim is to *prevent* CRC by detecting cancer precursors, then colonoscopy might be preferred
Polypectomy reduces Mortality

Standardized Incidence Mortality Ratio: 0.47

Expected from general population (SEER9)

Observed NPS adenoma cohort

Observed NPS nonadenoma cohort

Cumulative Colorectal Cancer Mortality (%)

No. at Risk

<table>
<thead>
<tr>
<th>Adenoma</th>
<th>Nonadenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>2602</td>
<td>773</td>
</tr>
<tr>
<td>2358</td>
<td>733</td>
</tr>
<tr>
<td>2100</td>
<td>678</td>
</tr>
<tr>
<td>1808</td>
<td>632</td>
</tr>
<tr>
<td>1246</td>
<td>420</td>
</tr>
<tr>
<td>461</td>
<td>164</td>
</tr>
</tbody>
</table>

Years Followed

15.8 yrs

25.4 deaths

12 deaths

Zauber et al; NEJM 2012; 366: 687-96
Questions posed

• Does FHX of adenoma change screening approach?
• Does age of patient change approach
• What type of screening – FIT or colonoscopy?
The questions behind the questions

• Is lifetime risk of CRC increased in individuals with family history of adenoma?
  – If index family member had advanced adenoma and is <60 years?
  – If index family member had advanced adenoma and is >60 years?
  – If index family member had LRA before or after age 60 years?
In the beginning....

- Common inheritance of susceptibility to adenomas and CRC (1988)
- National Polyp Study (1996)
  1031 patients with adenomas
    - 1865 parents
    - 2381 siblings
    - 1411 spouse controls

Cannon-Albright et al; NEJM 1988; 319: 533-7 (Burt)
Winawer et al; Risk of Colorectal cancer in families of patients with adenomatous polyps NEJM 1996; 334: 82-7
In the beginning....

- National Polyp Study
  - RR CRC (adjusted for age/sex): **1.78** (1.18-2.67) for parents/sibs c/w spouse controls
  - Adenoma <60 (vs >60): RR in sibs **2.59** (1.46-4.58)
  - Index sib with adenoma + parent with CRC:
    RR in sibs **3.25** (1.92-5.52)

- Conclusion:
  - Siblings and parents of patients with adenomas are at increased risk for CRC, especially if index <60 years

Winawer et al; NEJM 1996; 334: 82-7
Sniff test: Does this make sense?

• We now know that 50%+ of patients having screening colonoscopy have adenomas
  – This means that many, if not most people will have a FDR with adenoma

• 5-10% have advanced adenomas (>1cm; villous or HGD)
Sniff test: Does this make sense?

• 3121 patients enrolled for screening colonoscopy

<table>
<thead>
<tr>
<th>Finding at Screening Colonoscopy</th>
<th>OR for CRC in FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma-bearing vs patients with no adenomas</td>
<td>1.36 (1.09-1.70)</td>
</tr>
<tr>
<td>Small (&lt;1cm Tub Ad)</td>
<td>1.26 (0.99-1.61)</td>
</tr>
<tr>
<td>Advanced adenoma</td>
<td><strong>1.62 (1.16-2.26)</strong></td>
</tr>
</tbody>
</table>

Sniff test: Does this make sense?

- Question posed: does having a FDR with adenoma associated with increased risk of CRC?
  Only 2 relevant studies in 2012

<table>
<thead>
<tr>
<th>Finding at Screening Colonoscopy</th>
<th>Absolute risk for CRC in FDR</th>
<th>RR</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>2.31% vs 0.53%</td>
<td>4.38 (2.25-8.43)</td>
<td>Nakama; Eur J Cancer; 2000</td>
</tr>
<tr>
<td>Large adenoma</td>
<td>8.3% vs 4.2% (for CRC + Large adenoma)</td>
<td>1.97 (0.89-4.36)</td>
<td>Cottet; Gastroenterol 2007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Risk Measure (range): CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHX Adenoma vs no FHX of adenoma</td>
<td>1.35-1.78</td>
</tr>
<tr>
<td><strong>FDR with advanced adenoma or large adenoma (&gt;1cm)</strong></td>
<td>1.68-3.90</td>
</tr>
<tr>
<td>FDR &lt;60 years</td>
<td>1.41 (1.27-1.56)</td>
</tr>
</tbody>
</table>

Lowry et al; Cancer 2016; 122:2633-45
Family History: Current Guidelines

- Screening – Family History (non-hereditary)

<table>
<thead>
<tr>
<th>Index</th>
<th>Initiation</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDR &lt;60 CRC</td>
<td>Age 40 - colonoscopy</td>
<td>5 yrs</td>
</tr>
<tr>
<td>FDR &gt;60 CRC</td>
<td>Age 40 – any screen</td>
<td>10 yrs</td>
</tr>
<tr>
<td>FDR &lt; 60 with known advanced adenoma</td>
<td>Age 40 – colonoscopy</td>
<td>???</td>
</tr>
<tr>
<td>FDR: Non-advanced adenoma</td>
<td>50</td>
<td>routine</td>
</tr>
</tbody>
</table>

Evidence: Weak
What we think we know

• If there is \( \geq 1 \) FDR with **CRC**
  – Risk of CRC higher especially if index case \(<60\) yrs
  – Risk of advanced neoplasia higher...at a younger age
    – suggests there could be benefit of early screening
• If there is \( \geq 1 \) FDR with **advanced adenoma**
  – Risk of CRC is higher
  – Uncertain if CRC occurs at young age (i.e. \(<50\))
• If there is \( \geq 1 \) FDR with **low-risk adenoma**
  – Risk of CRC could be increased, but uncertain
What we would like to know

• FDR with **CRC and Advanced Adenoma**
  – Does early screening (before age 50 years) reduce incidence/mortality?
  – Is a shorter interval (q 5 years) between screenings associated with reduced incidence/mortality?
  – Should initiation and interval be customized based on age of index family member (i.e. > or < 60 years)?

• FDR with **low-risk adenoma**
  – Is the risk of CRC increased in family members?
  – Should screening be initiated at younger age?
  – Should screening with colonoscopy be preferred?
FHX and CRC: Summary

A riddle
Wrapped in a mystery
Inside an enigma...

Winston Churchill
New Practice Guideline 2017

• Sponsored by CAG

• Goals: Determine
  – Risk of CRC in families with Index member with CRC, and relationship of age and risk
  – Risk of CRC in families with Index member with adenoma, and relationship of type of adenoma, age, and risk
  – Use these data to understand
    • Age to initiate screening
    • Interval for screening if initial exam negative