Familial Risk in those with a First Degree Relative with an Advanced Adenoma

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Gastroenterology & Hepatology Fellow
University of Colorado Hospital
Advanced Adenoma

- Tubular adenoma $\geq 10\text{mm}$
- Adenoma with villous histology
- Adenoma with high grade dysplasia

Atkin et al. *NEJM* 1992
Winawer et al. *Cancer* 1992
Bond et al. *Am J Gastro* 2000
Risk to an individual who has a First Degree Relative (FDR) with:

- Colorectal Cancer (CRC)
- Any Adenoma
- Advanced Adenoma (AA)
## Risk of CRC if FDR has CRC

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th># studies</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns 2001</td>
<td>7</td>
<td>2.25 (2.25-2.53)</td>
</tr>
<tr>
<td>Baglietto 2006</td>
<td>7</td>
<td>2.81 (2.05-3.85)</td>
</tr>
<tr>
<td>Butterworth 2006</td>
<td>47</td>
<td>2.24 (2.06-2.43)</td>
</tr>
</tbody>
</table>

> 2 fold higher risk
RISK OF COLORECTAL CANCER IN THE FAMILIES OF PATIENTS WITH ADENOMATOUS POLyps

Siddney J. Winawer, M.D., Ann G. Zauber, Ph.D., Hans Gerdes, M.D., Michael J. O'Brien, M.D.,
Leonard S. Gottlieb, M.D., Stephen S. Sternberg, M.D., John H. Bond, M.D., Jerome D. Waye, M.D.,
Melvin Schapiro, M.D., Joel F. Panish, M.D., Robert C. Kurtz, M.D., Moshe Shike, M.D.,
Frederick W. Ackroyd, M.D., Edward T. Stewart, M.D., Mark Skolnick, Ph.D.,
D. Timothy Bishop, Ph.D., and THE NATIONAL POLYP STUDY WORKGROUP

Risk of CRC if FDR has any adenoma: RR 1.78 (95% CI 1.18-2.67)
Risk of CRC in siblings of those with any adenoma <60 years: RR 2.59 (95% CI 1.46-4.58)
Early screening if FDR has CRC

Early screening if FDR has adenoma

Early screening if FDR has advanced adenoma

1996 NPS

1997

2008

American College of Gastroenterology
American Gastroenterological Association
American Society for Gastrointestinal Endoscopy
American Cancer Society
American Society of Colon and Rectal Surgeons
Crohn’s and Colitis Foundation of America
Oncology Nursing Society
Society of American Gastrointestinal Endoscopic Surgeons

American College of Gastroenterology

Austin et al Clin Gastroenterol Hepatol 2011
CRC Screening in the United States

Early screening if FDR has CRC

Early screening if FDR has adenoma

Early screening if FDR has advanced adenoma

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2008

American College of Gastroenterology

2017

National Comprehensive Cancer Network
US Multi Society Task Force
American College of Gastroenterology
American Gastroenterological Association
American Society for Gastrointestinal Endoscopy
Case-Control Studies

**Exposure**
- + FDR with CRC
- No FDR with CRC

**Outcome**
- Cases: Adenoma/AA
- Controls: No adenoma/AA

**Intended Question**
- Do those with a FDR with adenoma have a higher risk for CRC?

**Actual Question**
- Do those with a FDR with CRC have a higher risk of adenoma
Case-Control Studies

**Exposure**
+ FDR with CRC

**Outcome**
Cases: Adenoma/AA
Controls: No adenoma/AA

**Intended Question**
- Do those with a FDR with adenoma have a higher risk for CRC?

**Actual Question**
- Do those with a FDR with CRC have a higher risk of adenoma?

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Cohort or Cross-Sectional Studies

**Exposure**
+ FDR with Adenoma/AA
No FDR with Adenoma/AA

**Outcome**
Colorectal cancer

- Do those with a FDR with adenoma/AA have a higher risk of CRC?
Risk of colorectal neoplasia in those with a FDR with a large adenoma

<table>
<thead>
<tr>
<th></th>
<th>Relatives (n=168)</th>
<th>Controls (n=307)</th>
<th>Adjusted* OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers or large adenomas</td>
<td>8.4%</td>
<td>4.2%</td>
<td>2.27 (1.01-5.09)</td>
</tr>
<tr>
<td>Cancers</td>
<td>3%</td>
<td>1%</td>
<td>3.9 (0.89-17.01)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and geographical area of relatives and controls
Risk of colorectal neoplasia in those with a FDR with a villous adenoma

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relatives (%)</th>
<th>Controls (%)</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Cancer</td>
<td>0.64%</td>
<td>0.41%</td>
<td>1.68 (1.29-2.18)</td>
</tr>
<tr>
<td>Advanced Adenoma</td>
<td>8.17%</td>
<td>5.18%</td>
<td>1.65 (1.28-2.14)</td>
</tr>
</tbody>
</table>
### Risk of colorectal neoplasia in siblings of those with AA

<table>
<thead>
<tr>
<th>Category</th>
<th>Matched Odds Ratio</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Adenomas</td>
<td>1.0</td>
<td>2.16</td>
<td>5.03</td>
</tr>
<tr>
<td>Any Adenoma</td>
<td>3.3 [2.16-5.03]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced Adenoma</td>
<td>6.1 [2.74-13.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25% Villous features</td>
<td>6.3 [2.02-19.53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma ≥10mm</td>
<td>8.6 [3.44-21.45]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Grade Dysplasia</td>
<td>20.0 [2.03-197]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Matched Odds Ratio

*Adjusted for age and sex of proband

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Ng et al. *Gastroenterology* 2016
## Guidelines

<table>
<thead>
<tr>
<th>United States Multi-Society Task Force (US MSTF)</th>
<th>Advanced adenoma in 2 FDRs (any age) or in 1 FDR &lt;60 years</th>
<th>Start at age 40 or 10 years before the age at diagnosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA in 1 FDR &gt; 60 years</td>
<td>Start at age 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Colonoscopy every 5y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>National Comprehensive Cancer Network (NCCN)</th>
<th>AA in 1 FDR (any age)</th>
<th>Start at age 40 or at age of onset of adenoma in relative*</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>• Colonoscopy every 5-10y</td>
</tr>
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</table>

*whichever is earlier
What about Advanced Serrated Polyps?

- Sessile Serrated Polyp (SSP) $\geq 10$ mm
- Sessile Serrated Polyp with Dysplasia
- Traditional Serrated Adenoma
Advanced Serrated Polyps: Large SSP

- Increased risk of synchronous advanced neoplasia
  OR 3.24 (95% CI 2.05-5.13)
- Increased risk of CRC 3.34 (95% CI 2.16-5.03)
- Need data on risk to FDR

Li et al Am J Gastro 2009
Hiraoka et al Gastroenterology 2010
“Screening for first-degree relatives of persons with advanced serrated lesions should be similar to the screening of FDRs with advanced conventional adenomas”

conditional recommendation, low quality evidence
Summary

- Risk in those with a FDR with CRC is >2 fold higher
- Risk in those with a FDR with AA is increased, but the exact magnitude of risk is not well defined
- Risk AA $\neq$ Risk Advanced Serrated Polyp
Challenges

- People don’t know family history of polyps
- Takes time! And resources!
- What magnitude of risk would warrant special screening?

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<th>Exposure</th>
<th>Outcome</th>
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<tr>
<td>+ FDR with Adenoma/AA</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>No FDR with Adenoma/AA</td>
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</tbody>
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- Do those with a FDR with adenoma/AA have a higher risk of CRC?
Acknowledgements

Dr. Dennis Ahnen
Dr. Swati Patel
NIH Training Grant T32 DK007038
Early Onset Colorectal Cancer

Hereditary 16%
Family History of CRC 14%
Sporadic

American Cancer Society 2018
Pearlmen et al JAMA Oncol 2017
Incidence of CRC by family history of CRC

**Graph:**
- **Y-axis:** Cumulative Incidence (cases/10,000)
- **X-axis:** Age (yr)
- Two curves:
  - **Family history**
  - **No family history**
- The curve for **family history** shows a higher incidence compared to **no family history**.