Hereditary GI Cancers: Chemoprevention and Risk Assessment

Elena M. Stoffel, MD MPH
Director, Cancer Genetics Clinic
Division of Gastroenterology
University of Michigan
Objectives

• Review role for chemoprevention in management of individuals with hereditary CRC
  – Open clinical trials

• Review pilot data for utility of risk assessment tools for identifying patients at increased risk for CRC
CRC in Michigan

Age-Adjusted Incidence Rates of Colorectal Cancer by Age Group in Michigan, 1999-2006

7-25% with germline mutations
“Red Flags” for Hereditary CRC

• Family History
  – Multiple cancers (CRC, endometrial, ovarian, breast, thyroid)

• Personal history
  – Young CRC (age<50)
  – Multiple primary cancers
  – CRCs arising after colonoscopy (interval cancers)
  – Multiple polyps
    • Adenomas: ≥10-20
    • Hamartomas: ≥3-5
    • Sessile Serrated: Multiple (>20), >5 large in proximal colon
    • Mixed polyp types (eg, ganglioneuromas)
Approaches to Genetic Risk Assessment

• Universal tumor testing of CRCs (and endometrial cancers) for Mismatch Repair

• Family History—How to implement in clinical settings?

• Personal history (cancers, polyps)
Prevalence of Germline Mutations in Patients with “Multiple” Adenomas

Impact of Genetic Diagnosis on Management

• Endoscopic surveillance
  – Types of exams (colonoscopy +/- EGD)
  – Interval (q 6 months to 2 years depending on polyp burden)

• Type of Surgery
  – Segmental colectomy
  – Subtotal Colectomy
  – Total Colectomy
    • Ileorectal anastomosis
    • Ileoanal anastomosis (J pouch)
Cancers After Colectomy--FAP

Rectal Remnant (IRA)
Defining Colonic Polyp Burden: Chromoendoscopy

>100 polyps
Upper GI Polyps in FAP
FAP Duodenal Adenomas: Spiegelman Stage

Stage I-II

Stage III

Stage IV
Management of Polyposis

- Endoscopic polypectomy

- Surgical Resection
  - Duodenal resection
  - Pancreatoduodenectomy (Whipple)

- Chemoprevention
  - Sulindac (clinoril), cox-2 inhibitors
  - clinical trials
Eflornithine (DFMO)

- Inhibitor of ornithine decarboxylase (polyamine synthesis pathway)

- Reduces intestinal polyps in APC min mouse model

- Human Phase III clinical trial demonstrated reduced incidence of sporadic adenomas
A Double-Blind, Randomized Phase III Trial of the Safety and Efficacy of CPP-1X/Sulindac Compared with CPP-1X, Sulindac as Single Agents in Patients with Familial Adenomatous Polyposis

- Industry-sponsored, multicenter study (USA, Europe)
- Randomized Trial Double-Blinded
  - 150 mg Sulindac + Placebo
  - 750 mg DFMO + Placebo
  - 150 mg Sulindac + 750 mg DFMO
- Eligibility Criteria
  - FAP (APC+) and ≥ 18 yrs
  - Disease at one or more sites:
    1. Intact colon (pre-colectomy)
    2. Rectal/Pouch Polyposis
    3. Duodenal Polyposis, Spiegelman 3 or 4

2-Year Trial
Endpoints—Surgery, Cancer, Excision of advanced adenoma
Aspirin for Chemoprevention in Hereditary CRC

• FAP—CAPP1 Trial, ASA 600mg qd (RCT)
  – Non-significant reduction in polyp number and size

• Lynch Syndrome—CAPP2, ASA 600mg qd
  – RCT 841 randomized
  – No reduction in risk for neoplasia during 30 month follow up
  – Long-term, 63% reduction in CRC incidence among aspirin users (difference of 16 cancers)

J. Burn Familial Cancer 2013
Chemoprevention for Lynch Syndrome

• “There are data suggesting aspirin may decrease CRC risk in Lynch Syndrome, however the data are not sufficiently robust to make a recommendation for standard use.”
  – NCCN 2014

  – Clinical Trials?
A Phase Ib Biomarker Trial of Naproxen in Patients at Risk for DNA Mismatch Repair Deficient Colorectal Cancer

• NCI-sponsored
  – MD Anderson (lead), Dana-Farber, University of Michigan
• Randomized, placebo-controlled trial
  – 440 mg Naproxen
  – 220 mg Naproxen
  – Placebo
• Eligibility Criteria
  – Lynch Syndrome (mutation positive) and age ≥ 18

6 month trial—Biomarker endpoint
Preventing Cancers: Early Identification of Patients at risk for Hereditary CRC

- Family History Assessment

- Online Risk Models
  - MMRPro, PREMM1,2,6

- How to integrate risk assessment in clinical settings?
Case

- An asymptomatic 30 year old woman asks when she should start colorectal cancer screening

- Family history is notable for mother who died of CRC at age 48

  - Options:
    - A. Colonoscopy at age 50
    - B. Colonoscopy at age 38, 10 years before age at dx
    - C. Colonoscopy now
Family History

PREMM 1,2,6 Score: 7.7%
Family History

- Prostate Ca, Age 80
- Breast Ca, Age 85
- Colon Ca, Age 50
- Stomach Ca, Age 70
- Colon Ca, Age 48
- Colon Ca, Age 40
- Breast Ca, Age 75
- CRC, Age 35

PREMM 1,2,6 Score: 41%
## 5 Question Screen

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Do you have a first degree relative (father, mother, siblings, child) with any of the following conditions?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Colon or rectal cancer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>- Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>If the answer is yes to any of the above, were they diagnosed before age 60?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2.</td>
<td>Do you have three or more relatives (this includes grandparents, aunts, uncles, cousins) with a history of colon or rectal cancer?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Do you have a first degree relative (father, mother, brother, sister, child) diagnosed with colon polyps before the age of 60?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Have you had any of the following conditions diagnosed before age 50?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Colon or Rectal Cancer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>- Colon or Rectal Polyps</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>- Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5.</td>
<td>Have you had a total of 10 or more colon polyps removed in your lifetime?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## 5 Question Screen

<table>
<thead>
<tr>
<th>1.</th>
<th>Do you have a first degree relative (father, mother, siblings, child) with any of the following conditions?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Colon or rectal cancer</td>
</tr>
<tr>
<td></td>
<td>- Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain</td>
</tr>
<tr>
<td></td>
<td>If the answer is yes to any of the above, were they diagnosed before age 60?</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Do you have three or more relatives (this includes grandparents, aunts, uncles, cousins) with a history of colon or rectal cancer?</td>
</tr>
<tr>
<td>3.</td>
<td>Do you have a first degree relative (father, mother, brother, sister, child) diagnosed with colon polyps before the age of 60?</td>
</tr>
<tr>
<td>4.</td>
<td>Have you had any of the following conditions diagnosed before age 50?</td>
</tr>
<tr>
<td></td>
<td>- Colon or Rectal Cancer</td>
</tr>
<tr>
<td></td>
<td>- Colon or Rectal Polyps</td>
</tr>
<tr>
<td></td>
<td>- Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain</td>
</tr>
<tr>
<td>5.</td>
<td>Have you had a total of 10 or more colon polyps removed in your lifetime?</td>
</tr>
</tbody>
</table>

Web-Based Family Cancer History Tool

- Elicits cancer type and age at diagnosis in FDR, SDR
- Piloted and validated in Cancer Genetics Clinic
- Roll-out in UMHS outpatient clinics – Integrate risk models
Risk Assessment at Colonoscopy

• 800 unselected colonoscopy patients

• 55% were above average risk
  – 7% met criteria for genetic evaluation
CRC in Michigan

Age-Adjusted Incidence Rates of Colorectal Cancer by Age Group in Michigan, 1999-2006

7-25% with germline mutations
Next Steps

Molecular characterization of CRC cases age<50
– Germline and tumor mutation profiling

Systematize Family History Assessments
Primary care (presymptomatic), Cancer Clinics

Chemoprevention
High, Moderate, Average risk populations
Thank You

• Cancer Genetics Clinic, University of Michigan
  – estoffel@med.umich.edu
  – 734-615-9712
Selected References

• NCCN Guidelines genetic/familial high-risk assessment: colorectal nccn.org, 2014


