Colonoscopy in High Risk Population and the Elderly

Presented By:
Frances B. Horenstein, MD
Licking Memorial Health Systems

Objectives

- To define what is considered ’high risk’ in developing colon cancer.
- To discuss screening strategies / recommendations in individuals or groups considered to have high colon cancer risk.

USPSTF vs Multi-Society Task Force

Table. Characteristics of Colorectal Cancer Screening Strategies[a]

Screening Method	Frequency[b]	Evidence of Efficacy	Other Considerations
Stool-Based Tests			
gFOBT	Every year	RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II)	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT[c]	Every year	Test characteristic studies: Improved accuracy compared with gFOBT Can be done with a single specimen	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT-DNA	Every 1 or 3 y[d]	Test characteristic studies: Specificity is lower than for FIT, resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test Improved sensitivity compared with FIT per single screening test	There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due to provider and patient concerns over the genetic component of the test
Direct Visualization Tests			
Colonoscopy[c]	Every 10 y	Prospective cohort study with mortality end point	Requires less frequent screening Screening and diagnostic follow-up of positive findings can be performed during the same examination
CT colonography[e]	Every 5 y	Test characteristic studies	There is insufficient evidence about the potential harms of associated extracolonic findings, which are common
Flexible sigmoidoscopy	Every 5 y	RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies	Test availability has declined in the United States
Flexible sigmoidoscopy with FIT[c]	Flexible sigmoidoscopy every 10 y plus FIT every year	RCT with mortality end point (subgroup analysis)	Test availability has declined in the United States Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy

Multi-Society Task Force:2017

ACG, AGA, ASGE

Tier 1
Colonoscopy every 10 years
Annual fecal immunochemical test
Tier 2
CT colonography every 5 years
FIT-fecal DNA every 3 years
Flexible sigmoidoscopy every 10 years (or every 5 years)
Tier 3
Capsule colonoscopy every 5 years
Available tests not currently recommended
Septin 9

USPSTF

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary. See the Clinical Considerations section and the Table for details about screening strategies.	A
Adults aged 76 to 85 years	The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history. • Adults in this age group who have never been screened for colorectal cancer are more likely to benefit. • Screening would be most appropriate among adults who 1) are healthy enough to undergo treatment if colorectal cancer is detected and 2) do not have comorbid conditions that would significantly limit their life expectancy.	C

Colorectal cancer risk assessment tool[5]
(Patient who answers yes to any question should have more comprehensive family history evaluation)
1. Do you have a first-degree relative (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?
Colon or rectal cancer
Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain
2. Have you had any of the following conditions diagnosed before age 50 years?
Colon or rectal cancer
Colon or rectal polyps
3. Do you have three or more relatives with a history of colon or rectal cancer?
(This includes parents, brothers, sisters, children, grandparents, aunts, uncles, and cousins)

American College of Gastro, Clinical Guideline:Hereditary GI Cancer Syndromes

(+) FAMILY HISTORY OF CRC AND ADVANCED POLYP

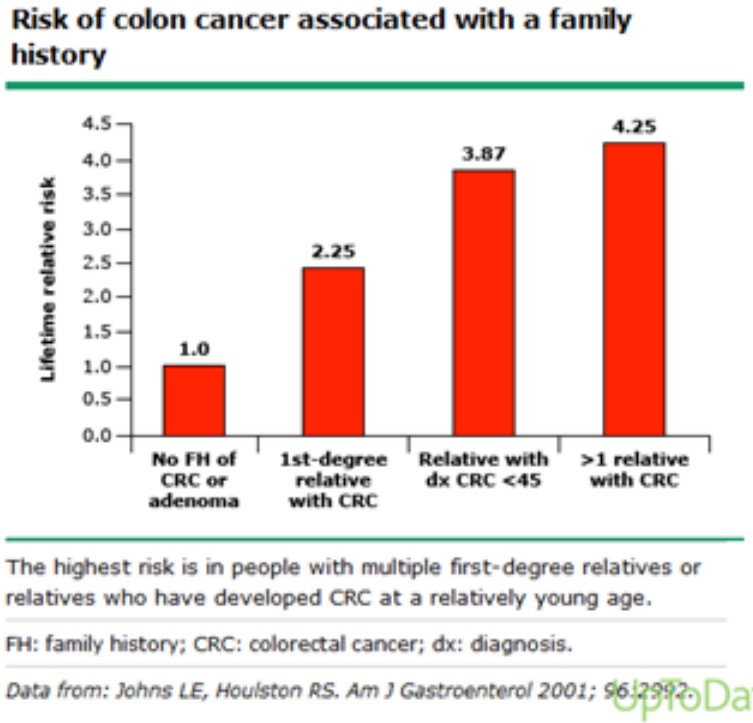
Family History of CRC

- First Degree Relative (FDR) 5-10% in the U.S.
  - Netherlands: 11.7% in ages 30-70
- Include number of FDR with CRC and age at diagnosis
- Most with family history of CRC: non familial

Highest Risk for Familial CRC

- multiple FDRs with CRC
- FDR who had

CRC <50 years of age



Family History of CRC

- Patients with CRC: 25% have a family history that placed them at increased risk.
- 45-75 y/o:11% with FDR with CRC had ADVANCED NEOPLASIA vs. 6% of those without FDR (OR 2.41; 95% CI 1.69-3.43)
- CRC in distant relatives or single FDR age >60: increase in risk is not large enough to warrant more screening than is recommended.

Family Polyp History

- FDR with adenomatous polyps MAY have increase risk for adenoma and CRC
- Limited data for history of adenoma and risk of CRC
- No evidence that a family history of non-advanced adenoma increases risk to the patient
- USMSTF:FDR with advanced polyp features or needing surgical excision->FDR with CRC
- FDR with an advanced serrated polyp: ???

Enhanced Screening in (+) FDR

- **FDR** diagnosed at age <60: screening at 40 or 10 years before FDR diagnosis; done every 5 years; annual FIT if declines colonoscopy
- >2 **FDR** diagnosed at any age: screening at age 40 or 10 years before the youngest FDR diagnosis; done every 5 years; annual FIT if declines colonoscopy
- One FDR diagnosed >60: Begin screening at age 40 years, using the same screening options as for *average-risk* patients, at the same frequency as for *average-risk* patients

HIGH RISK FAMILIAL CRC SYNDROMES

High Risk Familial CRC Syndromes

1. Lynch syndrome
2. Familial adenomatous polyposis (FAP)
3. MUTYH Associated Polyposis (MAP)
4. Juvenile Polyposis Syndrome
5. Cowden Syndrome
6. Attenuated FAP
7. Peutz-Jeghers Syndrome
8. Serrated Polyposis Syndrome

Table 5. Cumulative risks of colorectal cancer in hereditary colorectal cancer syndromes

Syndrome	Gene	Risk	Average age of diagnosis (years)	References
Sporadic cancer		4.8%	69	SEER(303)
Lynch syndrome	*MLH1/MSH2*	M: 27–74% F: 22–61%	27–60	(30–35,38)
	MSH6	M: 22–69% F: 10–30% M/F: 12%	50–63	(31,36,49,64)
	PMS2	M: 20% F: 15%	47–66	(37)
Familial adenomatous polyposis (FAP)	*APC*	100%	38–41	(81,123,126,316)
Attenuated FAP	*APC*	69%	54–58	(88,90,126,317–319)
MUTYH-associated polyposis	*MUTYH*	43–100%	48–50	(109,126,134,135,319)

Lynch Syndrome

- patients and families with a germline mutation in one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2) or the EPCAM gene
- HNPCC
  - hereditary nonpolyposis colorectal cancer
  - patients or families who fulfill the Amsterdam criteria

Lynch Syndrome

- a strong family history
  - multiple family members
  - across generations
  - CRC and other cancers at an early age
- *CRC patients without obvious family history can still have the syndrome and carry a Lynch Syndrome gene*
- Polyps: early age, increased tendency to develop into CRC

Table 4. Amsterdam criteria, revised Bethesda guidelines, and colorectal cancer risk assessment tool

Amsterdam criteria I (24)
At least three relatives with colorectal cancer (CRC); all of the following criteria should be present:
One should be a first-degree relative of the other two;
At least two successive generations must be affected;
At least one of the relatives with CRC must have received the diagnosis before the age of 50 years;
Familial adenomatous polyposis should be excluded;
Tumors should be verified by pathologic examination.
Amsterdam criteria II (24)
At least three relatives must have a cancer associated with Lynch syndrome (colorectal, cancer of the endometrium, small bowel, ureter, or renal–pelvis); all of the following criteria should be present:
One must be a first-degree relative of the other two;
At least two successive generations must be affected;
At least one relative with cancer associated with Lynch syndrome (LS) should be diagnosed before age 50;
Familial adenomatous polyposis should be excluded in the CRC case(s) (if any);
Tumors should be verified whenever possible.
Revised Bethesda guidelines (24)
Tumors from individuals should be tested for microsatellite instability (MSI) in the following situations:
CRC diagnosed in a patient who is younger than 50 years of age
Presence of synchronous, or metachronous, colorectal or other LS-related tumors[a], regardless of age
CRC with MSI-high histology[b] diagnosed in a patient who is younger than 60 years of age
CRC diagnosed in a patient with one or more first-degree relatives with an LS-related cancer, with one of the cancers being diagnosed under age 50 years
CRC diagnosed in a patient with two or more first- or second-degree relatives with LS-related cancer regardless of age

Lynch Syndrome: Screening

Consider genetic evaluation of the following individuals for Lynch syndrome:

- All newly diagnosed patients with CRC (alternatively, those diagnosed prior to age 70 years)
- Endometrial cancer prior to age 60 years
- First-degree relative of those with known MMR/*EPCAM* gene mutation
- Individuals with a CRC with a >5 percent chance of a MMR gene mutation by prediction models
- Family cancer history meeting Amsterdam I or II criteria or revised Bethesda guidelines

Screening Recommendations: Lynch Syndrome

- Colonoscopy every 1 to 2 years starting at 20-25 or 2-5 years prior to the earliest age of CRC diagnosis in the family
- MSH6/PMS2 mutations: start at 25-30 or 2-5 years prior to the earliest CRC
- Annual surveillance: not validated
- Endometrial and ovarian: pelvic exam with endometrial biopsy, US starting at 30-35

Familial Adenomatous Polyposis

- Autosomal dominant caused by APC gene mutations
- Classic: 100 or more adenomatous colorectal polyps
- Attenuated: few adenomas, later age of onset, 80% lifetime risk of CRC
- Risk of extracolonic malignancy

FAP Risk

- FDR with FAP
- >10-20 cumulative colorectal adenomas or adenomas in combination with extracolonic features assoc. with FAP
  - duodenal/ampullary adenomas
  - desmoid tumors
  - papillary thyroid cancer
  - epidermal cysts/osteomas

CRC Screening in FAP

- Classic
  - Colonoscopy or sigmoidoscopy 10-12 years old
  - annual surveillance
- Attenuated:
  - Colonoscopy yearly starting at age 25
- Colectomy: classic FAP and attenuated FAP with adenomas too numerous to resect by endoscopy

FAP:Extracolonic Malignancy Screening

- Gastric polyps/duodenal polyps: at the onset of colonic polyposis (25-30 y/o)
- Thyroid cancer: annual thyroid US starting in the late teens
- Desmoid tumors

Chemoprevention FAP

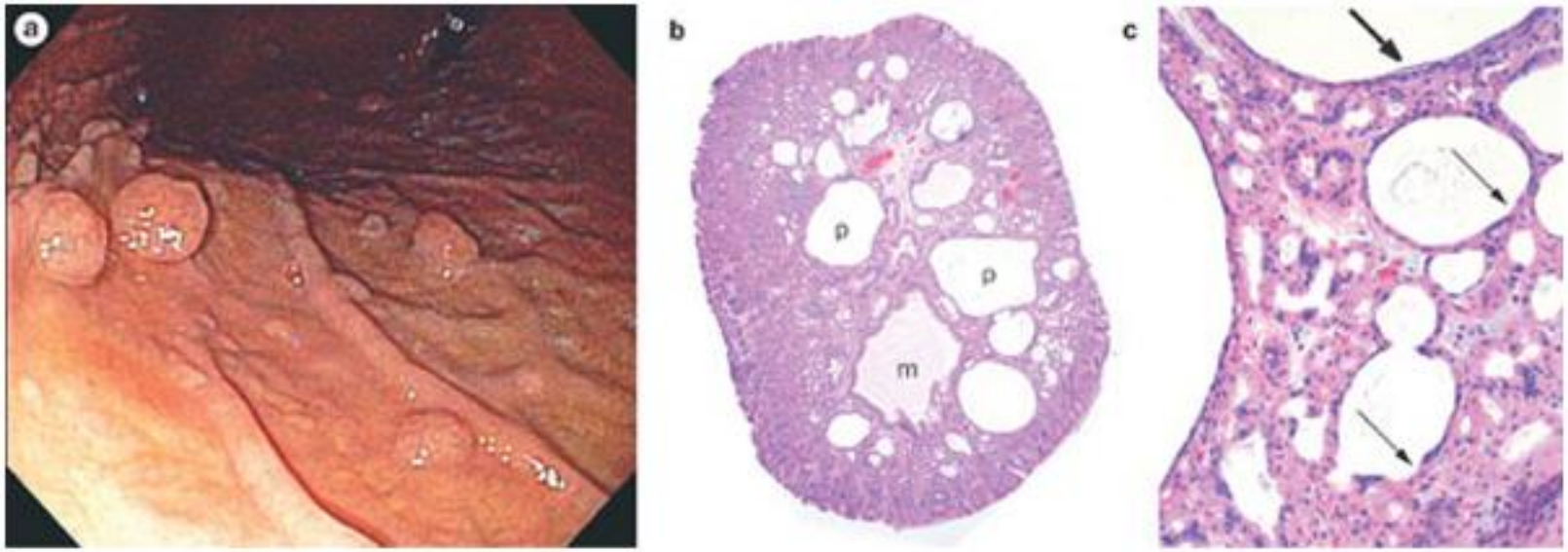
- Aspirin & NSAIDs: SULINDAC
- Erlotinib: epidermal growth factor inhibitor
- COX-2 inhibitors
- *Curcumin*

MUTYH-Assoc. Polyposis

- Autosomal recessive
- Multiple colorectal adenomas and increased risk of CRC (10-100)
- MUTYH: base excision repair gene
- Extracolonic: gastric and duodenal polyps; cancers of duodenum, ovaries, bladder, thyroid and skin

CRC Screening in MUTYH-Assoc. Polyposis

- Colonoscopy every 1-2 years starting at 25-30 years of age
- Surgical resection: high polyp burden and CRC
- Gastric and duodenal polyps: baseline EGD and duodenoscopy at 30-35 years old
- Thyroid: annual with physical exam and US (in patients with MUTYH-assoc polyposis)


a
b
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Serrated Polyposis Syndrome

- Hyperplastic Polyposis Syndrome
- Diagnostic Criteria:
  - at least 5 serrated polyps proximal to the sigmoid colon, with 2 or more >10mm
  - any number of serrated polyps in an individual with FDR with SPS
  - >20 serrated polyps of any size throughout the colon
- Genetic etiology is not defined

Surveillance for CRC in SPS

- Colonoscopy every 1-3 years with attempted removal of all polyps >5mm in diameter
- Extracolonic surveillance: no evidence

INFLAMMATORY BOWEL DISEASE

Ulcerative Colitis

- Pancolitis: 5-15 fold increase in risk of CRC
- Limited disease (L): 3x relative risk
- Proctitis or proctosigmoiditis: no increased risk
- CRC risk begins 8-10 years after disease onset in pancolitis and 15-20 years for left sided colitis
- Incidence of 0.5 % per year with disease duration of 10-20 years and 1% per year after

Crohn's Disease

- Risk comparable to UC if disease involves the colon
- CRC Surveillance at 8-10 years after disease onset with a colonoscopy.

Dealing With High Risk Patients

- Accurate risk assessment: age at CRC diagnosis, # of family members and relationship
- Presence of extracolonic malignancies in FDR or multiple family members
- Identify candidates for genetic testing
- Make recommendations on frequency of surveillance for CRC and other extraintestinal malignancies.