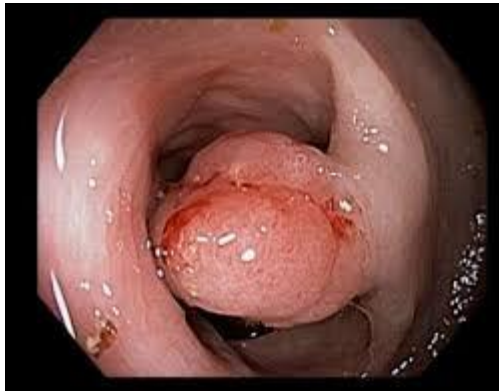
ZAHRA MOMAYEZ SANAT GASTROENTEROLOGIST



EPIDEMIOLOGY

CRC is the third most commonly diagnosed cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018 according to the World Health Organization GLOBOCAN database. Rates are substantially higher in males than in females.

Annually, approximately 53,200 Americans die of CRC, accounting for approximately 8 percent of all cancer deaths.

The incidence rates of gastrointestinal cancers are high in Iran (it is one of the known areas with a high incidence of GI cancers) younger cases are affected by an increasing rate of colorectal cancer in Iran, near the Western rates.

The highest incidence rates are in Australia and New Zealand, Europe, and North America, and the lowest rates are found in Africa and South-Central Asia . These geographic differences appear to be attributable to differences in dietary and environmental exposures that are imposed upon a background of genetically determined susceptibility.

Age is a major risk factor for sporadic CRC. Large bowel cancer is uncommon before the age of 40; the incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter .

Potentially modifiable behaviors such as physical inactivity, unhealthy diet, smoking, and obesity are thought to account for a substantial proportion

Over the last 50 years, a gradual shift toward right-sided or proximal colon cancers has been observed both in the United States and internationally, with the greatest increase in incidence in cecal primaries .

This change in the anatomic distribution of CRCs may be, in part, related to improvements in diagnosis and treatment, and increased screening with removal of adenomatous polyps in the distal colon

.. It is likely that part of the difference is due to aspects of quality relating to the colonoscopy (poor right-sided preps, incomplete colonoscopy, anatomic configurations compromising visibility) but the biology may also differ between CRCs of the right and left colon. For example, serrated adenomas, which are flatter and more difficult to visualize endoscopically,

CRC incidence is approximately 25 percent higher in men than in women and is approximately 20 percent higher in African Americans than in Whites

CRC Symptoms

Warning Signs of

COLON CANCER

You Shouldn't Ignore

1 CONSTIPATION

2 DIARRHEA

3 BLOOD IN STOOLS

4 NARROW STOOLS

5 UNEXPLAINED ANEMIA

6 TENDER ABDOMEN OR ABDOMINAL PAIN

7 UNEXPLAINED WEIGHT LOSS

8 WEAKNESS AND FATIGUE

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clinical manifestations also differ depending on tumor location:

- A change in bowel habits is a more common presenting symptom for left-sided than right-sided CRCs.

- Hematochezia is more often caused by rectosigmoid than right-sided colon cancer.

- Iron deficiency anemia from unrecognized blood loss is more common with right-sided CRCs .

- hematochezia or melena
- abdominal pain
- unexplained iron deficiency anemia
- change in bowel habits

Less common presenting symptoms include abdominal distention

, and/or nausea and vomiting, which may be indicators of obstruction

- **Abdominal pain can occur with tumors arising at all sites; it can be caused by a partial obstruction, peritoneal dissemination, or intestinal perforation leading to generalized peritonitis.**

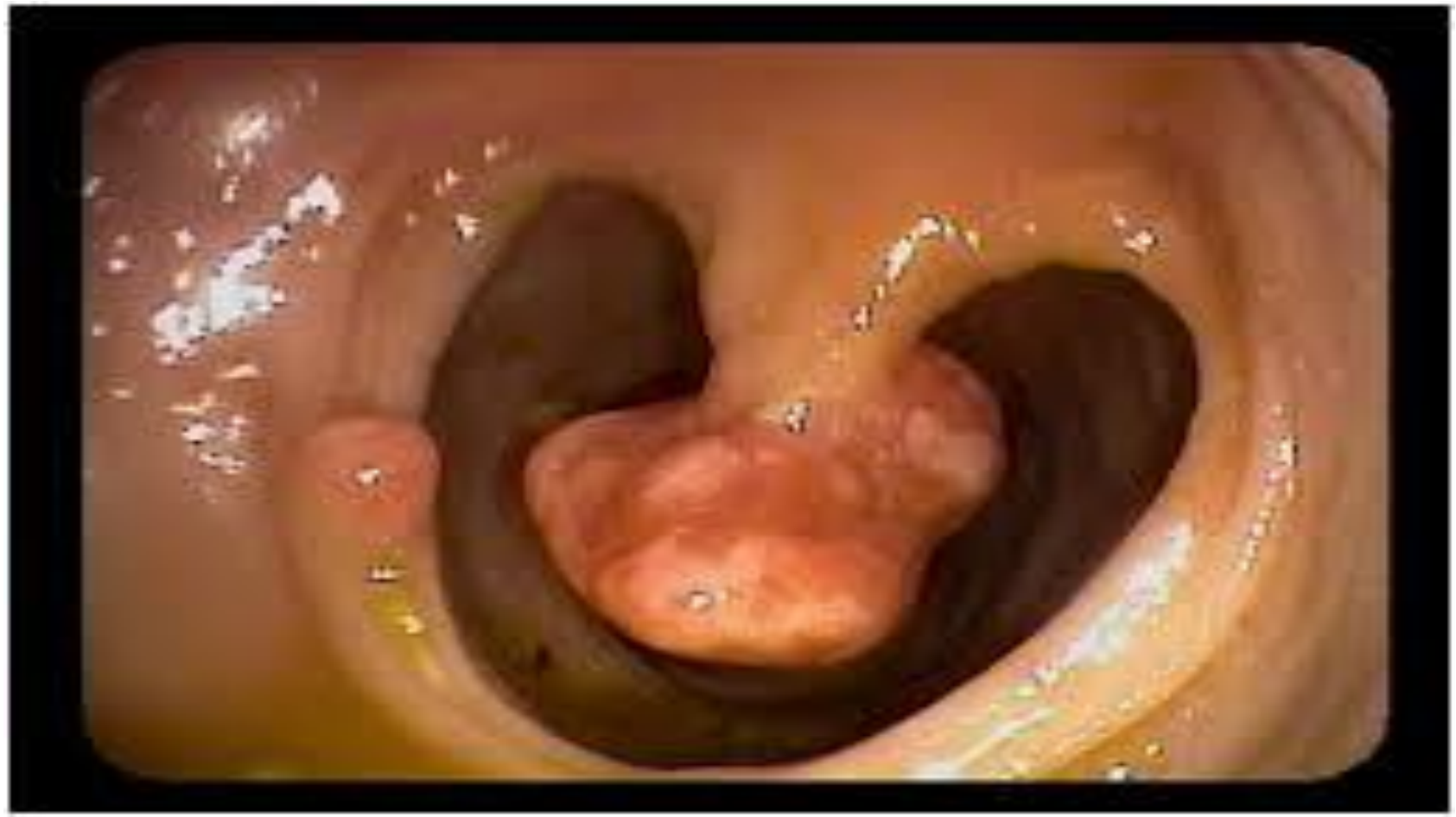
- **Rectal cancer can cause tenesmus, rectal pain, and diminished caliber of stools.**

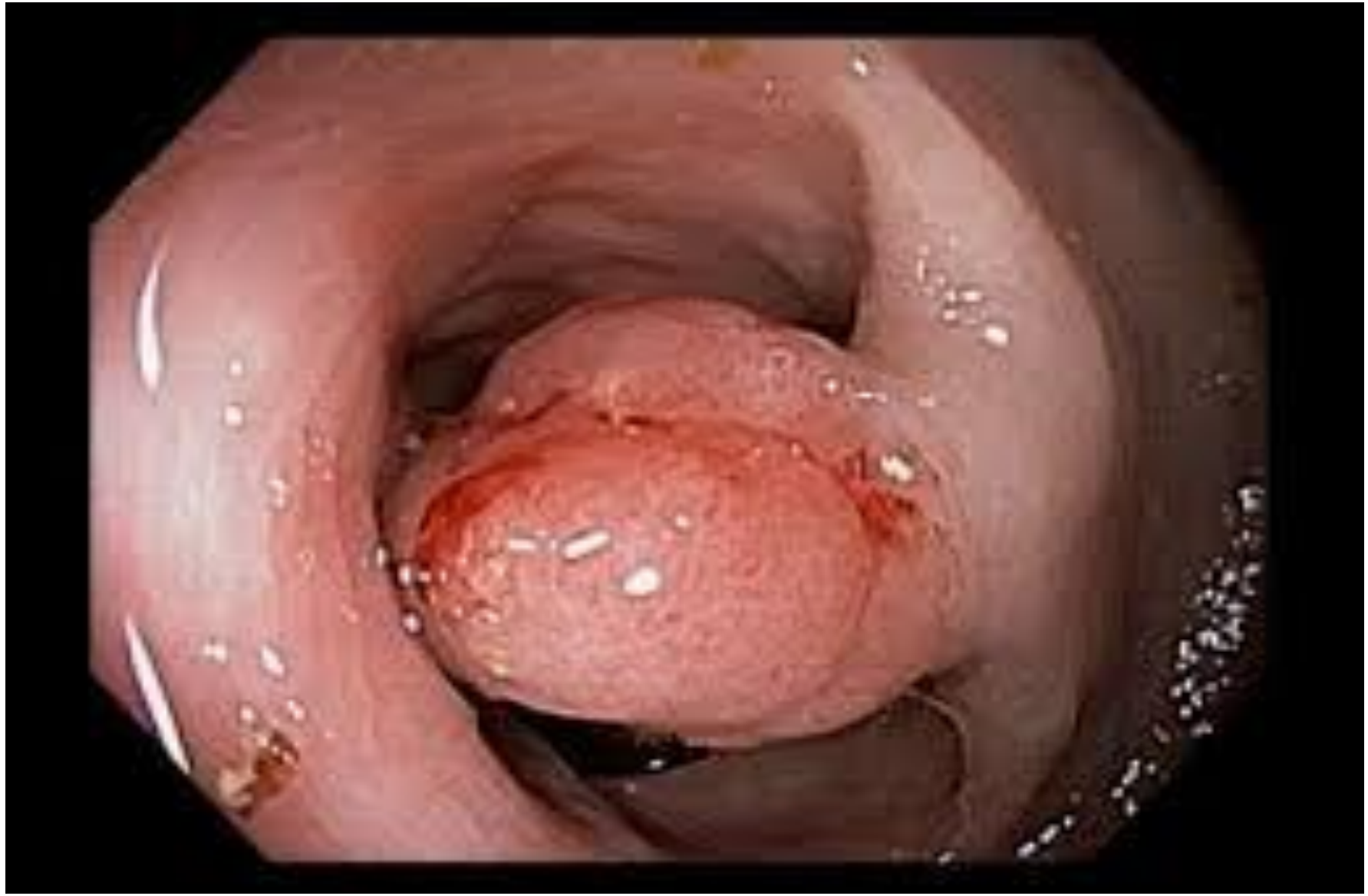
Patients may also present with signs/symptoms of metastatic disease

The most common metastatic sites are the regional lymph nodes, liver, lungs, and peritoneum.

Most colorectal cancers (CRC) arise from adenomatous colon polyps that progress from small (<8 mm) to large (≥8 mm) polyps, then to dysplasia and carcinoma

Progression from adenoma to carcinoma is believed to take an average of at least 10 years






COLON
CANCER

DIAGNOSIS

The diagnosis of a colorectal cancer (CRC) is made by histologic examination of a biopsy that is usually obtained during lower gastrointestinal tract endoscopy or from a surgical specimen. Histopathologically, the majority of cancers arising in the colon and rectum are adenocarcinomas

RISK FACTORS

Environmental and genetic factors can increase the likelihood of developing CRC

Hereditary CRC syndromes

Familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) are the most common of the familial colon cancer syndromes, but together these two conditions account for only approximately 5 percent of CRC cases, the majority of which are Lynch syndrome

Family history is also an important risk factor even outside of the syndromes with a defined genetic predisposition. Having a single affected first-degree relative (parent, sibling, or child) with CRC increases the risk approximately twofold over that of the general population . a first-degree relative is diagnosed below 50 years of age

advanced adenoma (≥1 cm, or high-grade dysplasia or villous elements)

Individuals who have a first-degree relative with a documented history of advanced adenoma should be screened similarly to those with a family history of CRC.

Factors that may influence screening recommendations

- **Race and gender**
- **Acromegaly**
- **Renal transplantation**

Risk factors that do not alter screening recommendations

- **Obesity**
- **Diabetes mellitus and insulin resistance**
- **Red and processed meat**
- **Tobacco**
- **Alcohol**
- **Use of androgen deprivation therapy**
- **Cholecystectomy**

SCREENING

Screening is intended for patients without signs or symptoms of possible CRC.

Benefits of screening

Screening tests for CRC can improve disease prognosis by identifying early-stage CRC that is easier to treat and has a lower mortality rate than CRC detected after symptoms develop. In addition, screening can prevent CRC by detecting and removing premalignant polyps before they progress to CRC.

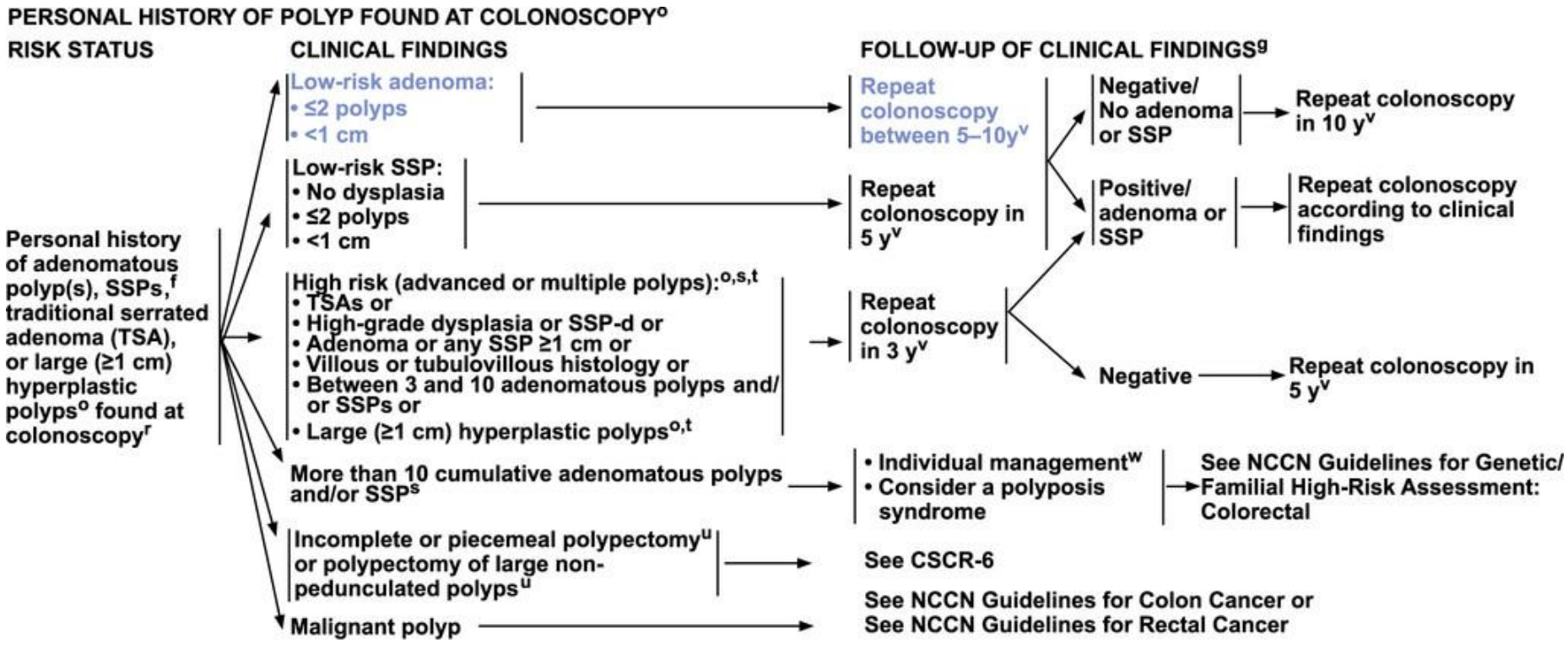
PROTECTIVE FACTORS

Physical activity

Diet

Fiber

The NCCN Guidelines for CRC Screening currently recommend that screening for average-risk individuals begin at 50 years of age.



[f] For details on classification, see footnote c on CSCR-1.
[g] See Screening Modality and Schedule (CSCR-A).
[o] There are limited data to support whether individuals with hyperplastic polyps ≥1 cm in size represent an increased risk group. Several analyses suggest that many of the larger polyps classified as hyperplastic in the past were re-classified as SSPs when reviewed by experts. For this reason, it is reasonable to follow patients with hyperplastic polyps ≥1 cm in size similarly to patients with SSPs, particularly if they have not been reviewed by an expert gastrointestinal pathologist.
[r] Surveillance colonoscopy is recommended in adults aged 50–75 years with a history of adenomas. Surveillance of individuals between ages 76–85 years should be individualized and include a discussion of risks and benefits of continued colonoscopy based on comorbidity status, estimated life expectancy, and findings on the last or the most recent colonoscopy.
[s] Ten or fewer polyps in the setting of a strong family history or younger age (<40 years) may sometimes be associated with an inherited polyposis syndrome.
[t] Surveillance intervals assume complete resection, adequate bowel preparation, and complete examination.
[u] Consider a referral to a center of expertise for large polyp management. For sessile polyps or LSL ≥20 mm size, recommend endoscopic tatoo placement for future lesion identificiation.
[v] Available data suggest that individuals with low-risk adenomas or SSPs may not have an increased risk of metachronous advanced colorectal neoplasia compared to the general population (Cottet V, et al. Gut 2012:61:1180-1186; He X, et al. Gastroenterol 2019; 158(4):852-861). Any recommendation for a shorter interval should include a discussion with the individual based on an assessment of individual risk, including age, family history, comorbidity, and the results of previous colonoscopies.
[w] If genetic testing is negative or if evaluation is not perfomed, repeat colonscopy within 3 years.

NCCN GUIDLINE

people who have one or more FDRs with CRC at any age, colonoscopy-based CRC

screening should start at age 40 years and be done every five years

if there is documentation that an FDR had an advanced adenoma (adenoma ≥1 cm, or with high-grade dysplasia, or with villous elements) or polyp requiring surgical excision, this should be weighted the same as having an FDR with CRC when suggesting screening programs

One or more FDR diagnosed at any age

Begin screening at age 40 years, or 10 years before the FDR's diagnosis, whichever is earlier (or in the case of an advanced polyp, at the age of diagnosis of the advanced polyp if that is earlier). We suggest colonoscopy every five years.

If the patient declines colonoscopy, annual fecal immunochemical testing (FIT) should be offered.

Choosing a screening test

Colonoscopy

Colonoscopy is the preferred test for patients at higher risk, as defined above . Among screening tests, colonoscopy has the highest sensitivity for CRC and for adenomas . If the patient refuses colonoscopy, FIT testing, considered by the US Multi-Society Task Force (MSTF) to be a "tier 1" test for CRC screening, is the suggested alternative and is performed annually

ADVANTAGE AND DISADVANTAGE

Among screening tests, colonoscopy has the highest sensitivity for CRC and adenomatous polyps and allows lesion removal anywhere in the colon during just one procedure with the potential to detect as well as prevent cancer by removing adenomatous polyps prior to malignant transformation.

- **Complications related to preparation**
- **Bleeding**
- **Perforation**
- **Complications related to sedation**

Colonoscopy is performed by a trained clinician using a flexible fiberoptic endoscope to directly visualize the inside of the rectum, colon, and a portion of the terminal ileum. Colonoscopy as a screening test is usually performed every 10 years for a patient at average risk of CRC and more frequently for a patient at higher risk

Colonoscopy has better sensitivity than FIT stool testing for advanced adenomas

Fecal immunochemical test (FIT) for blood

FIT directly measures hemoglobin in the stool.

FIT is performed on a small sample of stool that the patient provides in a special container. The frequency of testing varies in different locations, from annually

FIT requires only one stool sample and does not require restrictions to medications or diet prior to providing the sample; foods with peroxidase activity do not produce a false-positive FIT. Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) generally do not need to be temporarily discontinued to do a FIT test. In one observational study, FIT performance was better (higher sensitivity, only slightly lower specificity) among regular aspirin users compared with nonusers

Advantages and disadvantages

FIT is convenient for a patient to do. Dietary and medication restrictions are not needed. It does not require a bowel preparation, sedation, or time away from work or family (although if the FIT is positive, a colonoscopy will be advised for further evaluation). FIT requires only one sample rather than three days of samples as for guaiac-based fecal occult blood testing (gFOBT).

Because FIT is more convenient, it may have higher adherence. In a randomized trial of patients invited to participate in screening using one of three tests, participation rate was highest for FIT screening compared with FOBT or sigmoidoscopy (61 versus 49 versus 32 percent) .

FIT is more sensitive than gFOBT for colon lesions . In addition, a positive FIT has high specificity for lower gastrointestinal bleeding. However, FIT can be positive due to an upper gastrointestinal bleed that is large enough for hemoglobin to escape degradation during transit.

FECAL OB TEST

usually performed annually.

Guidelines generally recommend that gFOBT screening should only be performed using a highly sensitive guaiac reagent

Diet and medication use before and during testing

- A restrictive diet during gFOBT testing may not be necessary, although eliminating red meat for three days is recommended by the manufacturer . A systematic review found that advice to follow a restrictive diet did not reduce the gFOBT positivity rate, and restrictive diets decreased screening compliance .
- However, vitamin C intake should be restricted to <250 mg per day (which is less than the typical dose in a multivitamin) for at least three days prior to sampling . Large doses of vitamin C may cause false-negative tests .
- We do not ask patients to hold NSAIDs (including aspirin) or other antiplatelet therapy when collecting stool for gFOBT. While aspirin increases the risk for both upper and lower gastrointestinal bleeding and could decrease the PPV of gFOBT for significant colon disease, advice to hold these medications could deter patients from doing the screening test . By contrast, the manufacturer recommends that patients avoid NSAIDs (other than one aspirin per day) for seven days prior to the test

stool DNA tests with fecal immunochemical testing

stool composite of tests that include molecular assays to test for DNA (KRAS) mutations, a gene amplification technique to test for methylation biomarkers associated with colorectal neoplasia, and an immunochemical assay (FIT) to test for hemoglobin from blood that may be shed into the stool by colorectal lesions. DNA shed into the stool by colorectal neoplasms may reveal genetic mutations and epigenetic changes occurring during carcinogenesis

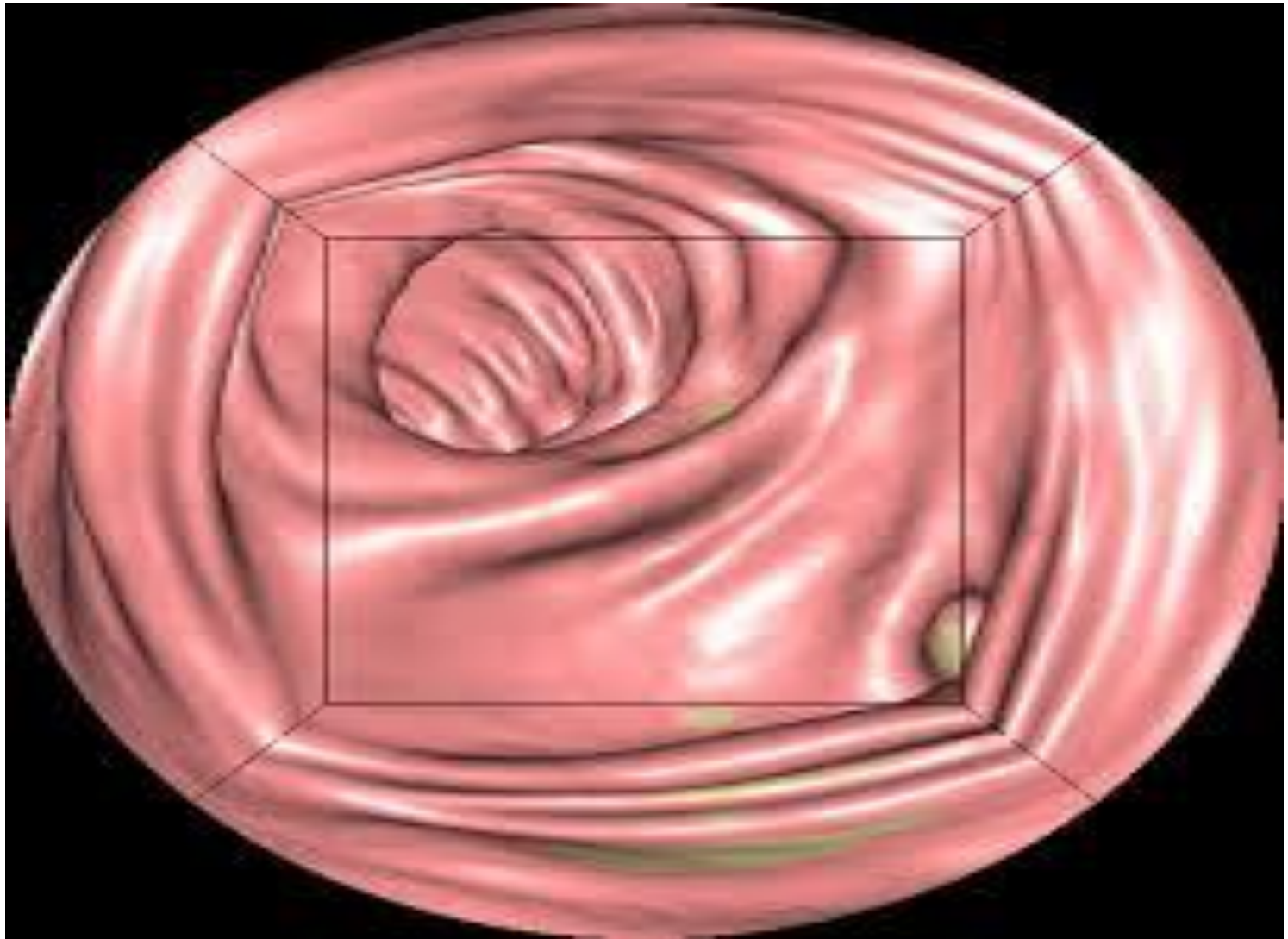
The test is performed every three years on one stool collection sample

Advantage and disadvantage

MT-sDNA testing has a higher single-application sensitivity and a lower specificity than FIT for CRC and advanced precancerous lesions , but it is more expensive than FIT.

MT-sDNA testing is included as a second-tier choice by MSTF and is also recommended by the ACS, NCCN, and USPSTF

Computed tomography colonography



Computed tomography colonography (CTC) involves obtaining multiple, thin-slice CT data and using computers to construct images of the bowel mucosa in two and three dimensions, with other enhancements to assist in interpretation.

Bowel preparation is required before the procedure. An intravenous catheter may be inserted to allow administration of drugs such as glucagon to relax the bowel, if needed. Air or carbon dioxide are introduced into the rectum via a catheter and typically cause cramping. Images are obtained during a single 32-second breath hold.

Sedation is not required. Patients undergoing CTC are exposed to radiation. If the CTC shows a colon lesion, a colonoscopy will be advised for further evaluation. Incidental radiologic findings in other organs may require additional testing.

CTC is performed every five years.

- **NCCN did not come to consensus about CTC for screening .**

Sigmoidoscopy

Sigmoidoscopy as a screening test is usually performed every five years. The 60 cm flexible fiberoptic sigmoidoscope reaches from the rectum up to the splenic flexure, allowing visualization of lesions, biopsy, and removal of polyps in the left-side of the colon only.

The sigmoidoscopy procedure can be done in an office setting without sedation.

Advantages and disadvantages

Sigmoidoscopy examines only the distal portion of the colon. However, 41 to 45 percent of CRCs are in the right side of the colon and may be missed on a sigmoidoscopy

There is also a shift toward a greater prevalence of right-sided lesions with age. Females have a higher percentage of right-sided colon lesions than males.

There is also a shift toward a greater prevalence of right-sided lesions with age. Females have a higher percentage of right-sided colon lesions than males.

Sigmoidoscopy combined with FIT (or sensitive gFOBT)

- **The combination of sigmoidoscopy with FIT or guaiac-based FOBT (gFOBT) theoretically enhances lesion detection by offering direct visualization up to 60 cm as well as by detecting colon lesions beyond the reach of a sigmoidoscope by testing for occult blood. FIT is preferred over sensitive gFOBT.**

The recommended frequencies of each test vary among expert guidelines.

USPSTF recommends sigmoidoscopy every 10 years with annual FIT, which is also an option in ASCO guidelines . NCCN includes an option for sigmoidoscopy every five years with annual FOBT . ACP includes sigmoidoscopy every five years plus combined FOBT or FIT every three years

DISCONTINUING SCREENING

We continue to screen for CRC through age 75 years for average-risk patients, as long as their life expectancy is 10 years or greater. Screening at least until age 75 years for patients at average risk for CRC is recommended by most guidelines . This is based on the increasing frequency of CRC with age and the time course of progression from polyp to CRC.

Although there is no direct evidence to guide when to end CRC screening among people with a family history, the MIcrosimulation SCreening Analysis (MISCAN)-Colorectal Cancer Model suggested that CRC screening should end at age 79 among persons with one FDR diagnosed after age 50, and end at age 85 for persons with two or more FDRs diagnosed before age 40 , unless the patient has a life expectancy less than 10 years. Continuing to screen until age 80 or 85 years is reasonable because the absolute risk of CRC attributable to family history increases with age, since the risk is cumulative

NCCN guidelines :

screening For patients who have a family history of colorectal cancer (CRC) or documented advanced adenoma

One or more FDR diagnosed at any age – Begin screening at age 40 years, or 10 years before the FDR's diagnosis, whichever is earlier (or in the case of an advanced polyp, at the age of diagnosis of the advanced polyp if that is earlier). We suggest colonoscopy every five years. If the patient declines colonoscopy, annual fecal immunochemical testing (FIT) should be offered.

If the patient declines colonoscopy, and FIT is used for screening, it is performed annually.

A personal history of adenomatous colorectal polyps increases the risk of CRC . The number and types of polyp lesions guide the determination of the appropriate interval for surveillance.

Individuals with an advanced adenoma should undergo a first surveillance colonoscopy in three years

Individuals with an nonadvanced adenoma should undergo a first surveillance colonoscopy in 5-10 years

Survillance for CRC

Colonoscopy at 1 year; subsequent studies dictated by prior findings. If no advanced adenoma, repeat at 3 years, then every 5 years; if advanced adenoma at 1 year, repeat at 1 year.

Flexible sigmoidoscopy with EUS or MRI every 3 to 6 months for 2 years, then every 6 months to complete 5 years for patients with rectal cancer undergoing transanal excision only.

Baseline colonoscopy finding	Recommended interval for surveillance colonoscopy	Strength of recommendation	Quality of evidence
Normal	10 years[¶]	Strong	High
1 to 2 tubular adenomas <10 mm	7 to 10 years[Δ]	Strong	Moderate
3 to 4 tubular adenomas <10 mm	3 to 5 years	Weak	Very low
5 to 10 tubular adenomas <10 mm	3 years	Strong	Moderate
Adenoma ≥10 mm	3 years	Strong	High
Adenoma with tubulovillous or villous histology	3 years[◊]	Strong	Moderate
Adenoma with high-grade dysplasia	3 years[◊]	Strong	Moderate
>10 adenomas on single examination[§]	1 year	Weak	Very low
Piecemeal resection of adenoma ≥20 mm	6 months	Strong	Moderate[¥]

Aspirin:

- There is substantial evidence about the protective effect of aspirin for CRC development when taken for at least 5–10 years.[4,5]
  - This led to the recommendation by the U.S. Preventive Services Task Force to endorse low-dose aspirin (81 mg) intake for individuals ages 50–59 with a ≥10% 10-year cardiovascular risk for the purposes of lowering both cardiovascular and CRC risk.
  - The decision to offer aspirin should take into consideration risk of bleeding, life expectancy, and long-term compliance.[6] The optimal dose has not been well established.
  - Regarding secondary prevention, aspirin use has been associated with improved CRC-specific survival and overall survival.[7]