

# Colorectal Cancer Screening and Prevention

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Colorectal cancer is a common cause of morbidity and mortality in the United States. Most colorectal cancers arise from pre-existing adenomatous or serrated polyps. The incidence and mortality of colorectal cancer can be reduced with screening of average-risk adults 50 to 75 years of age. Randomized controlled trials show evidence of reduced colorectal cancer-specific mortality with guaiac-based fecal occult blood tests and flexible sigmoidoscopy. There are no randomized controlled trials on the effectiveness of colonoscopy to reduce colorectal cancer-specific mortality; however, several randomized controlled trials comparing colonoscopy with other strategies are in progress. The best available evidence supporting colonoscopy is from prospective cohort studies that demonstrate decreased incidence of colorectal cancer and colorectal cancer-related mortality in individuals undergoing colonoscopy. Other screening options include fecal immunochemical testing, computed tomographic colonography, and multitargeted stool DNA testing combined with fecal immunochemical testing. There is good evidence that aspirin, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and hormone therapy decrease the risk of colorectal cancer and adenomatous polyps, but potential harms limit their usefulness. There is good evidence that calcium supplementation, moderate dairy consumption, reduced red meat consumption, increased physical activity, decreased body mass index, and statin use decrease the risk of colorectal cancer and adenomatous polyps. Although increased alcohol intake and tobacco use are associated with an increased risk of colorectal cancer, there is no direct evidence that reducing alcohol consumption or smoking cessation decreases the risk. (*Am Fam Physician*. 2018;97(10):658-665. Copyright © 2018 American Academy of Family Physicians.)

**Colorectal cancer** (CRC) is the third most common cancer and cause of cancer-related deaths in the United States.<sup>1</sup> Most CRCs are caused by adenomatous or serrated polyps as a result of sporadic mutations or DNA mismatch repair.<sup>2</sup> CRC screening reduces mortality by removing adenomatous and serrated polyps or by early detection of CRC; however, only 62% of eligible persons were up-to-date on CRC screening, according to the 2015 National Health Interview Survey.<sup>3,4</sup>

## Screening Guidelines

The U.S. Preventive Services Task Force (USPSTF) recommends CRC screening for average-risk adults 50 to 75 years of age.<sup>3</sup> The decision to screen adults 76 to 85 years of age

should be individualized based on overall health, previous screening, willingness to undergo treatment for CRC if found, and comorbid conditions.<sup>3</sup> Other guidelines are generally consistent (*Table 1*).<sup>3,5-9</sup>

The U.S. Food and Drug Administration recently approved a new serology test to detect circulating methylated SEPT9 DNA (Epi proColon), which is found in some CRCs.<sup>3</sup> A prospective study of 7,941 individuals found poor sensitivity (48%) with this test,<sup>10</sup> and it is not recommended by any U.S. cancer screening guidelines.

## Stool-Based Screening

Stool-based screening is quick, noninvasive, and can be done in the home.<sup>3</sup> Stool-based screening methods include guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), and multitargeted stool DNA test (FIT-DNA).<sup>3</sup> Of these, FIT-DNA is significantly more expensive than the other two.

gFOBT is the most common stool-based test for CRC screening worldwide. A 2013 Cochrane review of four randomized controlled trials (RCTs)

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**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 634.

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**Patient information:** A handout on this topic, written by the authors of this article, is available at <https://www.aafp.org/2018/0515/p658-s1.html>.

TABLE 1

## Summary of Colorectal Cancer Screening Recommendations for Average-Risk Persons\*

Organization	Recommendations
American Academy of Family Physicians <sup>5</sup>	<p>Screening for CRC with FIT, flexible sigmoidoscopy, or colonoscopy should start at 50 years of age and continue until 75 years of age.</p> <p>The decision to screen for CRC in adults 76 to 85 years of age should be individualized, taking into account the patient's overall health and screening history.</p> <p>Screening for CRC is not recommended in adults older than 85 years.</p>
American Cancer Society <sup>6</sup>	<p>Starting at 45 years of age and continuing through the age of 75 years, adults at average risk of CRC with a life expectancy of more than 10 years should undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. Clinicians should individualize screening decisions for individuals aged 76 through 85 years, and discourage individuals older than 85 years from continuing CRC screening.</p> <p>Options for CRC screening are:</p> <ul style="list-style-type: none"> <li>Fecal immunochemical test annually</li> <li>High-sensitivity, guaiac-based fecal occult blood test annually</li> <li>Multi-target stool DNA test every three years</li> <li>Colonoscopy every 10 years</li> <li>Computed tomographic colonography every five years</li> <li>Flexible sigmoidoscopy every five years</li> </ul>
American College of Gastroenterology <sup>7</sup>	<p>The preferred test is colonoscopy every 10 years, beginning at 50 years of age.</p> <p>Screening should begin at 45 years of age in blacks.</p> <p>FIT should be offered to patients who decline colonoscopy.</p>
Canadian Task Force on Preventive Health Care <sup>8</sup>	<p>Screening for CRC should start at 50 years of age and continue until 74 years of age using stool-based tests or direct visualization tests.</p> <p>Stool-based test: gFOBT or FIT every two years</p> <p>Direct visualization test: Flexible sigmoidoscopy every 10 years</p> <p>Colonoscopy is not recommended as a screening test for CRC.</p>
U.S. Multi-Society Task Force on Colorectal Cancer <sup>9</sup>	<p>Screening for CRC should begin at 50 years of age in average-risk persons; however, limited evidence supports screening beginning at 45 years of age in blacks. Discontinue screening at 75 years of age or in individuals who have a life expectancy less than 10 years.</p> <p>First-tier recommendation: Colonoscopy every 10 years or annual FIT</p> <p>Second-tier recommendation: Computed tomographic colonography every five years, FIT-DNA test every three years, or flexible sigmoidoscopy every five to 10 years</p> <p>Third-tier recommendation: Capsule colonoscopy every five years</p>
U.S. Preventive Services Task Force <sup>3</sup>	<p>Screening for CRC should start at 50 years of age and continue until 75 years of age.</p> <p>Stool-based tests:</p> <ul style="list-style-type: none"> <li>gFOBT every year</li> <li>FIT every year</li> <li>FIT-DNA test every one or three years</li> </ul> <p>Direct visualization tests:</p> <ul style="list-style-type: none"> <li>Colonoscopy every 10 years</li> <li>Computed tomographic colonography every five years</li> <li>Flexible sigmoidoscopy every five years</li> <li>Flexible sigmoidoscopy every 10 years with FIT every year</li> </ul>

CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac-based fecal occult blood test.

\*—An average-risk adult is defined as an asymptomatic person without a personal or family history of adenomatous polyps or other illness that predisposes to CRC (e.g., inflammatory bowel disease, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer).

Information from references 3, and 5 through 9.

BEST PRACTICES IN PREVENTIVE MEDICINE

Recommendations from the Choosing Wisely Campaign

Recommendation	Sponsoring organization
Do not repeat colorectal cancer screening (by any method) for 10 years after a high-quality colonoscopy is negative in average-risk individuals.	American Gastroenterological Association
Avoid colorectal screening tests on asymptomatic patients with a life expectancy of less than 10 years and no family or personal history of colorectal neoplasia.	American College of Surgeons
Do not recommend screening for breast, colorectal, prostate, or lung cancers without considering life expectancy and the risks of testing, overdiagnosis, and overtreatment.	American Geriatrics Society

**Source:** For more information on the Choosing Wisely Campaign, see <http://www.choosingwisely.org>. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see <https://www.aafp.org/afp/recommendations/search.htm>.

involving 329,642 individuals concluded that, compared with no screening, gFOBT screening reduced CRC-specific mortality after 11 to 30 years of follow-up (number needed to screen = 1,000).<sup>11</sup> gFOBT has fair sensitivity (62% to 79%) but good specificity (87% to 96%) for detecting CRC (positive likelihood ratio [LR+] = 4.7 to 19.8; negative likelihood ratio [LR-] = 0.2 to 0.4).<sup>3</sup> Screening with gFOBT should be performed yearly.<sup>3</sup> Individuals must submit three stool samples collected at home, and avoid heme-containing foods before the test. Office-based gFOBT is not recommended for CRC screening.

A 2014 meta-analysis of 19 cohort studies found that FIT is more sensitive and specific than gFOBT for detecting CRC.<sup>12</sup> FIT also has the advantages of not requiring any dietary restrictions and needing only a single stool sample. One RCT found that screening with immunochemical fecal occult blood testing had no significant impact on CRC mortality (relative risk = 0.88; 95% confidence interval [CI], 0.72 to 1.07).<sup>13</sup> FIT has good sensitivity (73% to 88%) and excellent specificity (91% to 95%) for detecting CRC (LR+ = 8.1 to 17.6; LR- = 0.1 to 0.3).<sup>3</sup> Screening with FIT also should be performed yearly.<sup>3</sup>

A FIT-DNA assay (ColoGuard) combines FIT with testing for altered DNA biomarkers.<sup>14</sup> A prospective study of 9,989 persons 50 to 84 years of age who underwent screening colonoscopy found that FIT-DNA was more sensitive (92% vs. 74%) but less specific (90% vs. 96%) than FIT alone for detecting CRC.<sup>15</sup> However, both FIT and FIT-DNA have poor sensitivity (24% and 42%, respectively) for detecting adenomatous polyps and serrated polyps measuring 1 cm or greater.<sup>3</sup> Screening with FIT-DNA should be performed

every one to three years, but it is reimbursed by Medicare only every three years.<sup>3</sup>

**Direct Visualization Screening**

Direct visualization tests, which include colonoscopy, computed tomographic colonography (CTC; also called virtual colonoscopy), and flexible sigmoidoscopy, allow for the identification of adenomatous polyps and serrated polyps before their natural progression to CRC. Polyps found during colonoscopy can be removed during the procedure, whereas polyps found using other methods require follow-up colonoscopy. Harms may occur during bowel preparation (e.g., dehydration, electrolyte imbalances), sedation or anesthesia for colonoscopy

(e.g., cardiovascular events), or the procedure itself (e.g., colonic perforations, bleeding).

Colonoscopy, the most widely used test for CRC screening in the United States, is typically performed in a hospital-based endoscopy suite or an ambulatory surgical center. It involves complete bowel preparation (e.g., polyethylene glycol [Golytely]), and is typically performed with sedation. There are no RCTs on colonoscopy to reduce CRC-specific mortality; however, several RCTs comparing colonoscopy with FIT or no screening are in progress.<sup>16,17</sup> A 2013 prospective cohort study of 88,902 participants in the Nurses' Health Study reported a 27% decreased incidence of CRC and a 68% decrease in mortality from CRC in individuals who had undergone a colonoscopy.<sup>18</sup> Screening with colonoscopy is recommended every 10 years in average-risk persons with normal findings and good bowel preparation.<sup>3</sup>

Serious risks of colonoscopy include cardiopulmonary complications (0.9%), bowel perforation (less than 0.1%), hemorrhage (0.1% to 0.6%), infection (less than 0.1%), and postpolypectomy syndrome (2.9%).<sup>19</sup> Postpolypectomy syndrome is characterized by abdominal pain, leukocytosis, and peritoneal inflammation in the absence of perforation after polypectomy with electrocoagulation; it may occur up to two weeks after polypectomy. A systematic review of six studies with 465 individuals found that the miss rate after colonoscopy was 2.1% for adenomatous polyps greater than 10 mm and 26% for adenomatous polyps 1 to 5 mm.<sup>20</sup> A population-based cohort study of 12,487 individuals reported the miss rate was 2% to 6% for CRCs.<sup>21</sup>

CTC is an alternative screening test, but supporting evidence is limited to studies of its test characteristics.

Radiation exposure from a single CTC is equivalent to 70 chest radiographs.<sup>22,23</sup> When used for screening, CTC requires bowel preparation but not administration of intravenous contrast media. A 2011 meta-analysis of five RCTs or cohort studies comparing CTC with colonoscopy in average-risk adults 50 years and older found that CTC has high sensitivity for adenomatous polyps greater than 10 mm.<sup>24</sup> Extracolonic findings have been reported in up to 70% of examinations, which is a potential harm because only 3% of these findings require treatment.<sup>3</sup> CTC has good sensitivity (67% to 94%) and very good to excellent specificity (86% to 98%) for detecting adenomatous polyps and serrated polyps measuring 1 cm or greater (LR+ = 4.8 to 47; LR- = 0.06 to 0.4).<sup>3</sup> Screening with CTC is recommended every five years.<sup>3</sup>

Flexible sigmoidoscopy may be performed in the office without sedation, but it requires bowel preparation. A 2013 Cochrane review of five RCTs with 414,754 individuals evaluated the effectiveness of flexible sigmoidoscopy in average-risk adults compared with no screening or with usual care.<sup>11</sup> This review found that, compared with no screening, flexible sigmoidoscopy lowers CRC mortality by 28% (95% CI, 21% to 35%).<sup>11</sup> A meta-analysis of five RCTs concluded that flexible sigmoidoscopy reduces the incidence of CRC (number needed to screen = 361 to prevent one case of CRC) and reduces CRC mortality (number needed to screen = 850).<sup>25</sup> One RCT including 98,792 individuals comparing flexible sigmoidoscopy plus gFOBT with flexible sigmoidoscopy alone concluded that there was no benefit to adding gFOBT in terms of CRC incidence or mortality.<sup>26</sup> A pooled analysis of three large RCTs including 287,928 individuals found that flexible sigmoidoscopy reduced the incidence of CRC and CRC mortality in men and in women younger than 60 years; however, this study concluded that alternative screening methods should be considered in women older than 60 years.<sup>27</sup> The USPSTF recommends screening with flexible sigmoidoscopy every five years.<sup>3</sup>

### Choosing a Test: Benefits, Harms, Burdens, and Costs

Family physicians can help their patients choose a test for CRC screening by reviewing test characteristics, benefits, harms, burdens, and costs. In addition to the advantages and disadvantages of each test, physicians must consider patient preference, comorbidities, test availability, likelihood that the test will be completed, and availability of resources for follow-up of abnormal test results. *Tables 2 and 3*<sup>3</sup> provide an overview of the tests recommended by the USPSTF. All approaches are thought to significantly decrease deaths caused by CRC (between 20 and 24 per 1,000 persons

screened, depending on the test), although complication rates and lifetime colonoscopy burden vary considerably.

### Prevention

*eTable A* summarizes colon cancer prevention strategies, including medications, lifestyle factors, and diet.

#### ASPIRIN

Although aspirin use decreases CRC incidence by 40%, a 2016 USPSTF guideline including three RCTs recommended against aspirin use in the average-risk population because of the risk of gastrointestinal bleeding and hemorrhagic stroke.<sup>28</sup> Individuals 50 to 59 years of age with a 10-year cardiovascular event risk of at least 10% who are willing to take aspirin for at least 10 years (i.e., the time it takes to accrue the cancer prevention benefit) may benefit from aspirin use for CRC risk reduction. A 2017 systematic review with meta-analysis found that the effect of aspirin was similar to FOBT and flexible sigmoidoscopy for reducing CRC incidence and mortality, and aspirin was more effective for cancers in the proximal colon.<sup>29</sup>

#### NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND CYCLOOXYGENASE-2 INHIBITORS

Studies show that nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors decrease the risk of CRC and adenomatous polyps; however, an increased risk of adverse effects outweighs potential benefits for most patients.<sup>30-33</sup>

#### LIFESTYLE FACTORS

Although studies have found an association between CRC and increased alcohol intake,<sup>34,35</sup> there is no direct evidence that decreasing alcohol consumption decreases the risk of CRC, adenomatous polyps, or serrated polyps. Cigarette smoking is associated with an increased risk of CRC and adenomatous polyps; a 2008 meta-analysis found that current smokers were more than twice as likely to develop high-risk adenomatous polyps or CRC.<sup>36</sup> However, there is a lack of evidence that smoking cessation decreases the risk of CRC, adenomatous polyps, or serrated polyps.

Reduction of body mass index may decrease the risk of CRC. A 2007 meta-analysis found an association between increasing body mass index and CRC,<sup>37</sup> and a 2014 meta-analysis found that bariatric surgery was associated with a 27% decreased risk of CRC compared with individuals with obesity who did not undergo the surgery.<sup>38</sup> Higher body mass index is also a risk factor for CRC mortality (hazard ratio = 1.03; 95% CI, 1.00 to 1.05).<sup>39</sup>

Increased physical activity is also associated with reduced risk of CRC. A 2017 meta-analysis showed that increased

TABLE 2

### Advantages, Disadvantages, and Costs of Colorectal Screening Tests

Description	CPT code	Advantages	Disadvantages	Cost*
Colonoscopy	45378	Ability to detect and remove polyps Visualizes the entire colon	Requires comprehensive bowel preparation Takes 20 to 30 minutes plus recovery time Patient may not drive or return to work if sedation is given	\$1,700
Computed tomographic colonography	74261	10- to 15-minute examination Noninvasive imaging of entire colon Sedation is not required Patient may drive and return to work after procedure	Requires bowel preparation similar to colonoscopy Requires rectal tube to insufflate air into colon, which may cause cramping Exposure to radiation May miss small or flat polyps Detection of extracolonic findings may lead to additional testing Positive test result requires colonoscopy	\$500
FIT	82274	At-home single stool sample Easy, safe, and convenient Not affected by diet or medications	Must be repeated annually Positive test result requires colonoscopy	NA
Flexible sigmoidoscopy	45330	Safer and more convenient than colonoscopy Takes about 10 minutes to complete Most patients may drive and return to work after procedure	Requires bowel preparation with enemas Only visualizes the distal third of colon Not typically done with sedation Positive test result requires colonoscopy	\$1,000
Guaiac-based fecal occult blood test	82270	At-home stool collection Easy, safe, and convenient	Must be repeated annually Requires dietary restrictions Requires three samples Positive test result requires colonoscopy	\$10
Multitargeted stool DNA test (FIT-DNA)	81528	At-home stool collection Easy, safe, and convenient Does not require dietary restrictions or bowel preparation	Expensive compared with other stool-based tests Positive test result requires colonoscopy	NA

CPT = Current Procedural Terminology; FIT = fecal immunochemical test; NA = not available.

\*—Estimated price per procedure based on information obtained at <https://www.healthcarebluebook.com>. Accessed December 18, 2017.

occupational and recreational activity were associated with a reduced risk of CRC.<sup>40</sup>

#### DIET

Although there is an association between increased fat intake and the risk of serrated polyps, there is no evidence that low-fat diets decrease risk. An RCT including 48,835 postmenopausal women 50 to 75 years of age found that women assigned to a low-fat diet did not have a lower risk of CRC than those assigned to usual diets after an eight-year follow-up.<sup>41</sup>

There is conflicting evidence on coffee consumption and the risk of CRC. The largest, most recent, and best-designed study is the Women's Health Initiative with 83,778 individuals. It found that moderate and high coffee intake (four or more cups per day) were associated with a small increase

in the risk of CRC (hazard ratio = 1.14 to 1.15).<sup>42</sup> However, another large meta-analysis of prospective cohort studies including 2,046,575 individuals found that the risk of colon cancer was decreased by 7% for every four cups of coffee consumed per day (relative risk = 0.93; 95% CI, 0.88 to 0.99;  $P = .199$ ).<sup>43</sup> Moderate intake of dairy (8 oz or more per day) is associated with a small decrease in the risk of CRC based on a 2004 meta-analysis.<sup>44</sup> Because of processing, it is difficult to separate data on dairy products from data on vitamin D and calcium.

Two Cochrane reviews found that increasing fiber intake did not lower the risk of CRC or recurrence of adenomatous polyps.<sup>45,46</sup> However, a reduction in red meat consumption is associated with a decreased risk of CRC. Previous meta-analyses found a modest increase in the risk of CRC associated with increased red meat consumption.<sup>47,48</sup>

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

### OTHER MEDICATIONS AND VITAMINS

Antioxidants should not be recommended to decrease the risk of CRC or adenomatous polyps. A 2013 meta-analysis of 20 RCTs including 268,590 individuals found that, compared with no treatment or placebo, there was no benefit of antioxidant use for reducing the risk of CRC or adenomatous polyps.<sup>49</sup>

Calcium supplementation decreases the risk of adenomatous polyps and is associated with a decreased risk of CRC in observational studies. A 2005 Cochrane review identified two randomized trials with 1,346 participants, and found a significant reduction in recurrent adenomatous polyps with calcium supplementation (odds ratio = 0.74; 95% CI, 0.58 to 0.95).<sup>50</sup> A 2016 analysis of two cohort studies demonstrated that total calcium intake of at least 1,400 mg per day compared with less than 600 mg per day was associated with a 22% reduced risk of CRC.<sup>51</sup> A 2017 meta-analysis that examined the effect of calcium on serrated polyps found no statistically significant effect.<sup>52</sup>

There is no evidence to support folic acid supplementation to decrease the risk of adenomatous polyps.<sup>53</sup> Although oral hormone therapy has been associated with a decreased risk of CRC in a case-control study, the harms outweigh potential benefits, and routine use is not

Clinical recommendation	Evidence rating	References
Colorectal cancer screening is recommended in average-risk adults 50 to 75 years of age.	<b>A</b>	3
Randomized controlled trials show evidence of reduced colorectal cancer–specific mortality with guaiac-based fecal occult blood testing (number needed to screen = 1,000) and flexible sigmoidoscopy screening (number needed to screen = 850).	<b>A</b>	11, 25
Aspirin, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and hormone therapy decrease the risk of colorectal cancer and adenomatous polyps; however, increased risks of adverse effects outweigh potential benefits for most patients.	<b>B</b>	28, 30-32, 52, 54
Calcium supplementation, increased dairy consumption, reduced red meat consumption, increased physical activity, decreased body mass index, and statin use are associated with a lower risk of colorectal cancer and adenomatous polyps, although most of the evidence is from observational studies.	<b>C</b>	37, 40, 44, 47, 48, 50-52, 55, 56
There is no evidence that antioxidants, fiber, or folic acid decreases the risk of colorectal cancer or adenomatous polyps.	<b>B</b>	45, 46, 49, 53

**A** = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <https://www.aafp.org/afpsort>.

**TABLE 3**

### Benefits, Harms, and Burdens of Colorectal Cancer Screening Tests Recommended by the U.S. Preventive Services Task Force

Test and interval	Years of life gained per 1,000 persons screened	Colorectal cancer deaths prevented per 1,000 persons screened	Complications per 1,000 persons screened	Lifetime colonoscopies per person screened
Colonoscopy every 10 years	270	24	15	4.0
Computed tomographic colonography every five years	248	22	10	1.7
FIT every year	244	22	10	1.8
FIT-DNA every year	261	23	12	2.7
FIT-DNA every three years	226	20	9	1.7
Flexible sigmoidoscopy every five years	221	20	10	1.8
Flexible sigmoidoscopy every 10 years plus FIT every year	256	23	12	2.3
Guaiac-based fecal occult blood test every year	247	22	11	2.3

FIT = fecal immunochemical test; FIT-DNA = multitargeted stool DNA test.

Information from reference 3.

recommended.<sup>54</sup> A 2017 meta-analysis did not find a statistically significant association between hormone therapy and the risk of serrated polyps.<sup>52</sup>

There is some evidence from observational studies that statin use is associated with a lower risk of advanced adenomatous polyps and CRC. However, data from RCTs are lacking.<sup>55,56</sup> Finally, there is conflicting evidence whether vitamin D supplementation decreases the risk of CRC or adenomatous polyps. A 2011 USPSTF report found no change in CRC risk in patients taking a vitamin D supplement.<sup>57</sup>

**This article** updates previous articles on this topic by Short, et al.<sup>58</sup>; Wilkins and Reynolds<sup>59</sup>; and Pignone and Levin.<sup>60</sup>

**Data Sources:** A clinical librarian completed a general PubMed search using the following MeSH terms: mass screening, colonoscopy, colorectal neoplasms, adenomatous polyp, colorectal cancer, primary prevention, and secondary prevention. These terms were also used as key words in a number of combinations. The search included meta-analyses, randomized controlled trials, and practice guidelines within the previous 20 years, and was expanded to reviews and clinical trials where needed. Reviews were hand-searched for further articles. Also searched were the Cochrane database and Essential Evidence Plus. Search dates: October 2016 and December 2017.

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eTABLE A

Summary of Factors for Prevention of Colorectal Cancer and Polyps

Factor	Effect	Comment	Evidence
<b>Diet</b>			
Cholesterol and fat intake	Twofold increased risk of CRC with increased cholesterol intake, and 25% increased risk of serrated polyps with increased fat intake	There is no evidence that reduction in cholesterol or fat intake lowers risk of CRC or serrated polyps	One meta-analysis, one RCT, and one prospective study <sup>A1-A3</sup>
Coffee consumption	Conflicting evidence	More research is needed from high-quality trials	One case-control study, one RCT, and one meta-analysis of prospective cohort studies <sup>A4-A6</sup>
Dairy intake	15% reduced risk of CRC with more than 8 oz of cow's milk per day	Moderate intake of cow's milk reduced risk of CRC	Meta-analysis of 10 cohort studies <sup>A7</sup>
Fiber	Increased fiber intake does not reduce the risk of CRC or recurrent adenomatous polyps	Fiber from different sources was used	Two Cochrane reviews and one meta-analysis of 13 prospective studies <sup>A8-A10</sup>
Red meat intake	22% increased risk of CRC with increasing red meat and processed meat intake	For every 3.5 oz of red meat intake per day, there was a 14% increased risk of CRC	Meta-analysis of 13 prospective studies and meta-analysis of 34 case-control studies and 14 cohort studies <sup>A11,A12</sup>
<b>Lifestyle</b>			
Alcohol intake	8% increased risk of CRC and 24% increased risk of serrated polyps	Evaluated effect of > 15 g per day of beer, wine, or spirits	Large cohort study (CRC) and meta-analysis of 10 observational studies (serrated polyps) <sup>A13,A14</sup>
Cigarette smoking	114% increased risk of high-risk adenomatous polyps and CRC in current smokers	Strong association between smoking and high-risk adenomatous polyps and CRC; no direct evidence that smoking cessation decreases risk	Meta-analysis of 42 observational studies <sup>A15</sup>
Obesity	Bariatric surgery associated with 27% reduced risk of CRC	Increasing body mass index associated with increased risk of colon cancer but not rectal cancer	Meta-analysis of four observational studies and a systematic review of 15 cohort studies <sup>A16-A18</sup>
Physical activity	26% decreased risk of colon cancer for occupational physical activity, and 20% decreased risk of colon cancer with recreational physical activity 12% decreased risk of rectal cancer for occupational physical activity, and 13% decreased risk of rectal cancer with recreational physical activity	Demonstrated benefit of increasing occupational and recreational physical activity for reducing the risk of colon and rectal cancers	Meta-analysis of 17 cohort studies and 21 case-control studies <sup>A19</sup>

*continues*

CRC = colorectal cancer; GI = gastrointestinal; RCT = randomized controlled trial.

## COLORECTAL CANCER

**eTABLE A** (continued)

### Summary of Factors for Prevention of Colorectal Cancer and Polyps

 (continued)

Factor	Effect	Comment	Evidence
<b>Medications</b>			
Antioxidants	No benefit for beta carotene; vitamins A, C, or E; or selenium	Not recommended to decrease the risk of CRC or adenomatous polyps	Meta-analysis of 20 RCTs <sup>A20</sup>
Aspirin	40% reduced risk of CRC	Not recommended in the average-risk population because of the risk of GI bleeding and hemorrhagic stroke	Review of three RCTs <sup>A21,A22</sup>
Calcium	26% reduced risk of adenomatous polyps and 22% reduced risk of CRC; no effect for serrated polyps	Calcium use for three to four years is recommended to decrease risk of CRC or adenomatous polyps but not serrated polyps	Cochrane review and meta-analysis <sup>A1,A23,A24</sup>
Cyclooxygenase-2 inhibitors	33% reduction of adenomatous polyps with use of celecoxib, and 35% reduction with use of rofecoxib (withdrawn from the market over safety concerns)	Not recommended secondary to increased risk of GI and cardiovascular events	Two RCTs <sup>A25-A27</sup>
Folic acid	Increased folic acid intake does not decrease risk of adenomatous polyps	Study examined effect of folic acid (1 mg per day) compared with placebo	RCT <sup>A28</sup>
Hormone therapy	63% reduced risk of CRC but no decreased risk of serrated polyps	Harms outweigh potential benefits, and routine use of hormone therapy is not recommended at this time	Meta-analysis of four studies and one case-control study <sup>A1,A29</sup>
Nonsteroidal anti-inflammatory drugs	63% decreased risk of CRC	Not recommended secondary to increased risk of GI and cardiovascular events	Meta-analysis of 15 RCTs <sup>A30</sup>
Statins	Statin use associated with 17% decreased risk of advanced adenomatous polyps and 50% decreased risk of CRC	Effect observed in individuals who had used a statin for at least five years	Meta-analysis of six studies and one case-control study <sup>A31,A32</sup>
Vitamin D	Guideline from U.S. Preventive Services Task Force found no benefit in vitamin D supplementation to decrease risk of CRC; a meta-analysis found 50% decreased risk of CRC or adenomatous polyps	Conflicting evidence that vitamin D supplementation decreases risk of CRC or adenomatous polyps	Guideline based on three RCTs and 28 observational studies, and meta-analysis of 18 observational studies <sup>A33,A34</sup>

*continues*

CRC = colorectal cancer; GI = gastrointestinal; RCT = randomized controlled trial.

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eTABLE A (continued)

**Summary of Factors for Prevention of Colorectal Cancer and Polyps** (continued)

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