Colorectal Cancer Prevention (PDQ®)–Health Professional Version

Go to Patient Version

Who Is at Risk?

For most people, the major factor that increases a person's risk for colorectal cancer (CRC) is advancing age. Risk increases dramatically after age 50 years; 90% of all CRCs are diagnosed after this age. Incidence and mortality rates are higher in African American individuals compared with other races. However, a meta-analysis found no evidence that African American individuals have higher rates of precancerous lesions.[1,2] The history of CRC in a first-degree relative, especially if diagnosed before the age of 55 years, roughly doubles the risk. A personal history of CRC, high-risk adenomas, or ovarian cancer also increase the risk.[3] Other risk factors for CRC have weaker associations than age and family history. People with inflammatory bowel disease, such as ulcerative colitis or Crohn disease, have a much higher risk of CRC starting about 8 years after disease onset and are recommended to have frequent colonoscopic surveillance.[4] A small percentage (<5%) of CRCs occur in people with a genetic predisposition, including familial adenomatous polyposis and Lynch syndrome (hereditary nonpolyposis CRC).

References

1. Imperiale TF, Abhyankar PR, Stump TE, et al.: Prevalence of Advanced, Precancerous Colorectal Neoplasms in Black and White Populations: A Systematic Review and Meta-analysis. Gastroenterology 155 (6): 1776-1786.e1, 2018. [PUBMED Abstract]
2. Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, et al.: Contribution of screening and survival differences to racial disparities in colorectal cancer rates. Cancer Epidemiol Biomarkers Prev 21 (5): 728-36, 2012. [PUBMED Abstract]
3. Imperiale TF, Juluri R, Sherer EA, et al.: A risk index for advanced neoplasia on the second surveillance colonoscopy in patients with previous adenomatous polyps. Gastrointest Endosc 80 (3): 471-8, 2014. [PUBMED Abstract]
4. Laukoetter MG, Mennigen R, Hannig CM, et al.: Intestinal cancer risk in Crohn's disease: a meta-analysis. J Gastrointest Surg 15 (4): 576-83, 2011. [PUBMED Abstract]

Overview

Note: The Overview section summarizes the published evidence on this topic. The rest of the summary describes the evidence in more detail.

Other PDQ summaries on Colorectal Cancer Screening; Colon Cancer Treatment; and Rectal Cancer Treatment are also available.

Factors With Adequate Evidence of Increased Risk of Colorectal Cancer

Excessive alcohol use

Based on solid evidence from observational studies, excessive alcohol use is associated with an increased risk of colorectal cancer (CRC).[1,2]

Magnitude of Effect: A pooled analysis of eight cohort studies estimated an adjusted relative risk (RR) of 1.41 (95% confidence interval [CI], 1.16–1.72) for consumption exceeding 45 g/day.[1]

Study Design: Cohort studies.

Internal Validity: Fair.

Consistency: Fair.

External Validity: Fair.

Cigarette smoking

Based on solid evidence, cigarette smoking is associated with increased incidence of and mortality from CRC.

Magnitude of Effect: A pooled analysis of 106 observational studies estimated an adjusted RR (current smokers vs. never smokers) of 1.18 for developing CRC (95% CI, 1.11–1.25).[3,4]

Study Design: 106 observational studies.

Internal Validity: Fair.

Consistency: Good.

External Validity: Good.

Obesity

Based on solid evidence, obesity is associated with increased incidence of and mortality from CRC.

Magnitude of Effect: In one large cohort study, the adjusted RR of developing colon cancer for women with a body mass index greater than 29 was 1.45 (95% CI, 1.02–2.07).[5,6] A similar increase in CRC mortality was found in another large cohort study.[7,8]

Study Design: Large cohort studies.

Internal Validity: Fair.

Consistency: Good.

External Validity: Good.

Family/personal history of colorectal cancer and other hereditary conditions

Based on solid evidence, a family history of CRC in a first-degree relative or a personal history of CRC increases the risk of CRC.[9-12] Having a genetic predisposition, including familial adenomatous

polyposis and Lynch syndrome (hereditary nonpolyposis CRC), also increases risk of CRC.[13]

Magnitude of Effect: In individuals with familial adenomatous polyposis, the risk of CRC by age 40 can be as high as 100%. Individuals with Lynch syndrome can have a lifetime risk of CRC of about 80%.

Study Design: Case-control and cohort studies.

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

For more information about family history and hereditary conditions, see Genetics of Colorectal Cancer.

Factors With Adequate Evidence for a Decreased Risk of Colorectal Cancer

Physical activity

Based on solid evidence, regular physical activity is associated with a decreased incidence of CRC.

Magnitude of Effect: A meta-analysis of 52 observational studies found a statistically significant 24% reduction in CRC incidence (RR, 0.76; 95% CI, 0.72–0.81).[14]

Study Design: Cohort studies and meta-analysis.

Internal Validity: Fair.

Consistency: Good.

External Validity: Good.

Interventions With Adequate Evidence for a Decreased Risk of Colorectal Cancer

Aspirin: Benefits

Based on solid evidence, daily aspirin (acetylsalicylic acid [ASA]) reduces CRC incidence and mortality after 10 to 20 years. This is based on three individual participant-level data meta-analyses of trials of aspirin used for the primary and secondary prevention of cardiovascular disease.[15-17]

Magnitude of Effect: ASA use reduces the long-term risk of developing CRC by 40% about 10 to 19 years after initiation (hazard ratio [HR], 0.60; 95% CI, 0.47–0.76).[18] Daily doses of 75 to 1,200 mg of ASA reduce the 20-year risk of CRC death by approximately 33% (HR, 0.67; 95% CI, 0.52–0.86).[16,17]

Study Design: Individual patient-level data meta-analyses of randomized controlled trials (RCTs) of ASA for primary and secondary cardiovascular prevention.

Internal Validity: Fair, some data from registries and death certificates, some loss to follow-up; variations in ASA dose and timing; adherence to ASA unknown after end of trials (5–9 years); trials designed to answer a different primary hypothesis (cardiovascular disease prevention).

Consistency: Generally consistent.

External Validity: Fair, most data (>75%) from men.

Aspirin: Harms

Based on solid evidence, harms of ASA use include excessive bleeding, including gastrointestinal bleeding and hemorrhagic stroke.

Magnitude of Effect: Very low-dose ASA use (i.e., ≤100 mg every day or every other day) results in an estimated 14 (95% CI, 7–23) additional major gastrointestinal bleeding events and 3.2 (95% CI, -0.5 to 0.82) extra hemorrhagic strokes per 1,000 individuals over 10 years. These risks increase with advancing age.[19]

Study Design: Evidence obtained from RCTs, cohort studies, and meta-analyses comparing ASA with placebo or no treatment for the primary prevention of cardiovascular disease.[19]

Internal Validity: Fair, data are from clinically and methodologically heterogeneous trials.

Consistency: Good.

External Validity: Fair, data on specific subgroups are limited.

Hormone therapy (estrogen plus progestin): Benefits

Based on solid evidence, combined hormone therapy (conjugated equine estrogen and progestin) decreases the incidence of invasive CRC.[20]

Based on fair evidence, combination conjugated equine estrogen and progestin has little or no benefit in reducing mortality from CRC. Data from the Women's Health Initiative (WHI), a randomized, placebo-controlled trial evaluating estrogen plus progestin, with a mean intervention of 5.6 years and a follow-up of 11.6 years, showed that women taking combined hormone therapy had a statistically significant higher stage of cancer (regional and distant) at diagnosis but not a statistically significant number of deaths from CRC compared with women taking the placebo.[20]

Magnitude of Effect: There were fewer CRCs in the combined hormone therapy group than in the placebo group (0.12% vs. 0.16%; HR, 0.72; 95% CI, 0.56–0.94). A meta-analysis of cohort studies observed a RR of 0.86 (95% CI, 0.76–0.97) for incidence of CRC associated with combined hormone therapy.

There were 37 CRC deaths in the combined hormone therapy arm compared with 27 deaths in the placebo arm (0.04% vs. 0.03%; HR, 1.29; 95% CI, 0.78–2.11).

Study Design: RCT and cohort studies.

Internal Validity: Good.

Consistency: Good for effect on incidence; not applicable (N/A) for effect on mortality; results were based on one trial.

External Validity: Good.

Hormone therapy (estrogen plus progestin): Harms

Based on solid evidence, harms of postmenopausal combined estrogen-plus-progestin hormone use include increased risk of breast cancer, coronary heart disease, and thromboembolic events.

Magnitude of Effect: The WHI showed a 26% increase in invasive breast cancer in the combined hormone group, a 29% increase in coronary heart disease events, a 41% increase in stroke rates, and a twofold higher rate of thromboembolic events.[21]

Study Design: Evidence from RCTs.

Internal Validity: Good.

Consistency: Good.

External Validity: Fair.

Polyp removal: Benefits

Based on fair evidence, removal of adenomatous polyps reduces the risk of CRC. Much of this reduction likely comes from removal of large (i.e., >1.0 cm) polyps, while the benefit of removing smaller polyps—which are much more common—is unknown. Some but not all observational evidence indicates that this reduction may be greater for left-sided CRC than for right-sided CRC.[22-24]

Magnitude of Effect: Unknown, probably greater for larger polyps (i.e., >1.0 cm) than for smaller ones.[25]

Study Design: Evidence obtained from cohort studies and one RCT of sigmoidoscopy.[23]

Internal Validity: Good.

Consistency: Consistent.

External Validity: Good.

Polyp removal: Harms

Based on solid evidence, the major harms of polyp removal include perforation of the colon and bleeding.

Magnitude of Effect: Seven to nine events per 1,000 procedures.[26-28]

Study Design: Evidence from retrospective cohort studies.[27,28]

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Factors With Inadequate Evidence of an Association With Colorectal Cancer

Nonsteroidal anti-inflammatory drugs (NSAIDs): Benefits

There is inadequate evidence that the use of NSAIDs reduces the risk of CRC. In people without genetic predisposition but with a prior history of a colonic adenoma that had been removed, three RCTs found that celecoxib [29,30] and rofecoxib [31] decreased the incidence of recurrent adenoma, although follow-up was too short to determine whether CRC incidence or mortality would have been affected.

Based on solid evidence, NSAIDs reduce the risk of adenomas, but the extent to which this translates into a reduction of CRC is uncertain.[32]

Study Design: No adequate studies with CRC outcome.

Internal Validity: N/A.

Consistency: N/A.

External Validity: N/A.

NSAIDs: Harms

Based on solid evidence, harms of NSAID use are relatively common and potentially serious, and include upper gastrointestinal bleeding, chronic kidney disease, and serious cardiovascular events such as myocardial infarction, heart failure, and hemorrhagic stroke.[33] A recent report compared the cyclooxygenase-2 (COX-2) inhibitor celecoxib (200 mg/d) with the nonselective nonsteroidals naproxen (850 mg/d) and ibuprofen (2,000 mg/d) in individuals with severe arthritis (i.e., not using lower doses as for primary prevention). The results showed that serious cardiovascular events were not less common for those taking the nonselective nonsteroidals. However, this study did not assess the comparative safety of lower doses or the safety of the COX-2 inhibitor rofecoxib.[34]

Magnitude of Effect: The estimated average excess risk of upper gastrointestinal complications in average-risk people attributable to NSAIDs is 4 to 5 per 1,000 people per year.[35,36] The excess risk varies with the underlying gastrointestinal risk; however, it likely exceeds ten extra cases per 1,000 people per year in more than 10% of users.[37] Serious cardiovascular events are increased by 50% to 60%.[36]

Study Design: Evidence obtained from RCTs and high-quality systematic reviews and meta-analyses.[35,36]

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

Calcium supplementation

The evidence is inadequate to determine whether calcium supplementation reduces the risk of CRC.

Dietary factors

There is no reliable evidence that a diet started in adulthood that is low in fat and meat and high in fiber, fruits, and vegetables reduces the risk of CRC by a clinically important degree.

Factors and Interventions With Adequate Evidence of no Association With Colorectal Cancer

Estrogen-only therapy: Benefits

Based on fair evidence, conjugated equine estrogens do not affect the incidence of or mortality from invasive CRC.[38]

Magnitude of Effect: N/A.

Study Design: Evidence from RCTs.

Internal Validity: Good.

Consistency: Good.

External Validity: Fair.

Statins: Benefits

Based on solid evidence, statins do not reduce the incidence of or mortality from CRC.

Study Design: Meta-analyses of RCTs.[39-41]

Internal Validity: Good.

Consistency: Good.

External Validity: N/A.

Statins: Harms

Based on solid evidence, the harms of statins are small.

Study Design: Observational studies,[42] multiple RCTs, and a review.[43]

Internal Validity: Good.

Consistency: Good.

External Validity: Good.

References

1. Cho E, Smith-Warner SA, Ritz J, et al.: Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med 140 (8): 603-13, 2004. [PUBMED Abstract]
2. Fedirko V, Tramacere I, Bagnardi V, et al.: Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol 22 (9): 1958-72, 2011. [PUBMED Abstract]
3. Botteri E, Iodice S, Bagnardi V, et al.: Smoking and colorectal cancer: a meta-analysis. JAMA 300 (23): 2765-78, 2008. [PUBMED Abstract]
4. Liang PS, Chen TY, Giovannucci E: Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer 124 (10): 2406-15, 2009. [PUBMED Abstract]
5. Martínez ME, Giovannucci E, Spiegelman D, et al.: Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 89 (13): 948-55, 1997. [PUBMED Abstract]
6. Giovannucci E, Ascherio A, Rimm EB, et al.: Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 122 (5): 327-34, 1995. [PUBMED Abstract]
7. Calle EE, Rodriguez C, Walker-Thurmond K, et al.: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348 (17): 1625-38, 2003. [PUBMED Abstract]

8. Ma Y, Yang Y, Wang F, et al.: Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One 8 (1): e53916, 2013. [PUBMED Abstract]

9. Johns LE, Houlston RS: A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 96 (10): 2992-3003, 2001. [PUBMED Abstract]

10. Schoen RE, Razzak A, Yu KJ, et al.: Incidence and mortality of colorectal cancer in individuals with a family history of colorectal cancer. Gastroenterology 149 (6): 1438-1445.e1, 2015. [PUBMED Abstract]

11. Butterworth AS, Higgins JP, Pharoah P: Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer 42 (2): 216-27, 2006. [PUBMED Abstract]

12. Samadder NJ, Curtin K, Tuohy TM, et al.: Increased risk of colorectal neoplasia among family members of patients with colorectal cancer: a population-based study in Utah. Gastroenterology 147 (4): 814-821.e5; quiz e15-6, 2014. [PUBMED Abstract]

13. Mork ME, You YN, Ying J, et al.: High Prevalence of Hereditary Cancer Syndromes in Adolescents and Young Adults With Colorectal Cancer. J Clin Oncol 33 (31): 3544-9, 2015. [PUBMED Abstract]

14. Wolin KY, Yan Y, Colditz GA, et al.: Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer 100 (4): 611-6, 2009. [PUBMED Abstract]

15. Flossmann E, Rothwell PM; British Doctors Aspirin Trial and the UK-TIA Aspirin Trial: Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 369 (9573): 1603-13, 2007. [PUBMED Abstract]

16. Rothwell PM, Wilson M, Elwin CE, et al.: Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 376 (9754): 1741-50, 2010. [PUBMED Abstract]

17. Rothwell PM, Fowkes FG, Belch JF, et al.: Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 377 (9759): 31-41, 2011. [PUBMED Abstract]

18. Chubak J, Whitlock EP, Williams SB, et al.: Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force. Ann Intern Med 164 (12): 814-25, 2016. [PUBMED Abstract]

19. Whitlock EP, Burda BU, Williams SB, et al.: Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med 164 (12): 826-35, 2016. [PUBMED Abstract]

20. Simon MS, Chlebowski RT, Wactawski-Wende J, et al.: Estrogen plus progestin and colorectal cancer incidence and mortality. J Clin Oncol 30 (32): 3983-90, 2012. [PUBMED Abstract]

21. Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288 (3): 321-33, 2002. [PUBMED Abstract]

22. Brenner H, Hoffmeister M, Arndt V, et al.: Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst 102 (2): 89-95, 2010. [PUBMED Abstract]

23. Atkin WS, Edwards R, Kralj-Hans I, et al.: Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 375 (9726): 1624-33, 2010. [PUBMED Abstract]

24. Brenner H, Chang-Claude J, Seiler CM, et al.: Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 154 (1): 22-30, 2011. [PUBMED Abstract]

25. Robertson DJ, Greenberg ER, Beach M, et al.: Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 129 (1): 34-41, 2005. [PUBMED Abstract]

26. Nelson DB, McQuaid KR, Bond JH, et al.: Procedural success and complications of large-scale screening colonoscopy. Gastrointest Endosc 55 (3): 307-14, 2002. [PUBMED Abstract]

27. Levin TR, Zhao W, Conell C, et al.: Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med 145 (12): 880-6, 2006. [PUBMED Abstract]

28. Warren JL, Klabunde CN, Mariotto AB, et al.: Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 150 (12): 849-57, W152, 2009. [PUBMED Abstract]

29. Bertagnolli MM, Eagle CJ, Zauber AG, et al.: Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 355 (9): 873-84, 2006. [PUBMED Abstract]

30. Arber N, Eagle CJ, Spicak J, et al.: Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 355 (9): 885-95, 2006. [PUBMED Abstract]

31. Lanas A, Baron JA, Sandler RS, et al.: Peptic ulcer and bleeding events associated with rofecoxib in a 3-year colorectal adenoma chemoprevention trial. Gastroenterology 132 (2): 490-7, 2007. [PUBMED Abstract]

32. Chudy-Onwugaje K, Huang WY, Su LJ, et al.: Aspirin, ibuprofen, and reduced risk of advanced colorectal adenoma incidence and recurrence and colorectal cancer in the PLCO Cancer Screening Trial. Cancer 127 (17): 3145-3155, 2021. [PUBMED Abstract]

33. Bresalier RS, Sandler RS, Quan H, et al.: Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 352 (11): 1092-102, 2005. [PUBMED Abstract]

34. Nissen SE, Yeomans ND, Solomon DH, et al.: Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 375 (26): 2519-29, 2016. [PUBMED Abstract]

35. Rostom A, Dubé C, Lewin G, et al.: Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med 146 (5): 376-89, 2007. [PUBMED Abstract]

36. Kearney PM, Baigent C, Godwin J, et al.: Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 332 (7553): 1302-8, 2006. [PUBMED Abstract]

37. Hernández-Díaz S, García Rodríguez LA: Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. BMC Med 4: 22, 2006. [PUBMED Abstract]

38. Ritenbaugh C, Stanford JL, Wu L, et al.: Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. Cancer Epidemiol Biomarkers Prev 17 (10): 2609-18, 2008. [PUBMED Abstract]

39. Baigent C, Keech A, Kearney PM, et al.: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins.

Lancet 366 (9493): 1267-78, 2005. [PUBMED Abstract]

40. Dale KM, Coleman CI, Henyan NN, et al.: Statins and cancer risk: a meta-analysis. JAMA 295 (1): 74-80, 2006. [PUBMED Abstract]

41. Browning DR, Martin RM: Statins and risk of cancer: a systematic review and metaanalysis. Int J Cancer 120 (4): 833-43, 2007. [PUBMED Abstract]

42. Hippisley-Cox J, Coupland C: Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 340: c2197, 2010. [PUBMED Abstract]

43. Joy TR, Hegele RA: Narrative review: statin-related myopathy. Ann Intern Med 150 (12): 858-68, 2009. [PUBMED Abstract]

Incidence and Mortality

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide [1] and the second leading cause of cancer deaths in men and women combined in the United States.[2] It is estimated that there will be 154,270 new cases diagnosed in the United States in 2025 and 52,900 deaths caused by this disease.[2] Between 2012 and 2021, incidence rates for CRC in the United States declined by about 1% per year overall. However, this declining incidence is confined to individuals aged 65 years and older. Between 2012 and 2021, incidence rates increased by 2.4% per year in individuals younger than 50 years and by 0.4% per year in individuals aged 50 to 64 years.[2] For the past 50 years, the mortality rate for CRC has been declining in both men and women. Over the last decade, the mortality rate declined by 1.7% per year.[2] Incidence and mortality rates are higher in Black individuals than in those of other races; however, a meta-analysis found no evidence that Black individuals have higher rates of precancerous lesions.[3-5]

The 5-year overall survival rate is 64% for CRC. About 4% of Americans are expected to develop CRC within their lifetimes.[2,6] The risk of CRC begins to increase after the age of 40 years and rises sharply at ages 50 to 55 years; the risk doubles with each succeeding decade and continues to rise exponentially. Despite advances in surgical techniques and adjuvant therapy, there has been only a modest improvement in survival for patients who present with advanced neoplasms.[7,8] Effective primary and secondary preventive approaches must be developed to reduce the morbidity and mortality from CRC.

References

1. Bray F, Laversanne M, Sung H, et al.: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74 (3): 229-263, 2024. [PUBMED Abstract]

2. American Cancer Society: Cancer Facts and Figures 2025. American Cancer Society, 2025. Available online. Last accessed January 16, 2025.

3. Imperiale TF, Abhyankar PR, Stump TE, et al.: Prevalence of Advanced, Precancerous Colorectal Neoplasms in Black and White Populations: A Systematic Review and Meta-analysis. Gastroenterology 155 (6): 1776-1786.e1, 2018. [PUBMED Abstract]

4. Laiyemo AO, Doubeni C, Pinsky PF, et al.: Race and colorectal cancer disparities: health-care utilization vs different cancer susceptibilities. J Natl Cancer Inst 102 (8): 538-46, 2010. [PUBMED Abstract]
5. Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, et al.: Contribution of screening and survival differences to racial disparities in colorectal cancer rates. Cancer Epidemiol Biomarkers Prev 21 (5): 728-36, 2012. [PUBMED Abstract]
6. Surveillance Research Program, National Cancer Institute: SEER*Explorer: An interactive website for SEER cancer statistics. Bethesda, MD: National Cancer Institute. Available online. Last accessed December 30, 2024.
7. Moertel CG, Fleming TR, Macdonald JS, et al.: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 322 (6): 352-8, 1990. [PUBMED Abstract]
8. Krook JE, Moertel CG, Gunderson LL, et al.: Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 324 (11): 709-15, 1991. [PUBMED Abstract]

Definition of Prevention

Primary prevention involves the use of medications or other interventions before the clinical appearance of colorectal cancer (CRC) with the intent of preventing clinical CRC and CRC mortality.

Etiology and Pathogenesis of Colorectal Cancer

Genetics,[1,2] experimental,[3,4] and epidemiologic [5-7] studies suggest that colorectal cancer (CRC) results from complex interactions between inherited susceptibility and environmental factors. The exact nature and contribution of these factors to CRC incidence and mortality is the subject of ongoing research.

References

1. Willett W: The search for the causes of breast and colon cancer. Nature 338 (6214): 389-94, 1989. [PUBMED Abstract]
2. Fearon ER, Vogelstein B: A genetic model for colorectal tumorigenesis. Cell 61 (5): 759-67, 1990. [PUBMED Abstract]
3. Reddy B, Engle A, Katsifis S, et al.: Biochemical epidemiology of colon cancer: effect of types of dietary fiber on fecal mutagens, acid, and neutral sterols in healthy subjects. Cancer Res 49 (16): 4629-35, 1989. [PUBMED Abstract]
4. Reddy BS, Tanaka T, Simi B: Effect of different levels of dietary trans fat or corn oil on azoxymethane-induced colon carcinogenesis in F344 rats. J Natl Cancer Inst 75 (4): 791-8, 1985. [PUBMED Abstract]
5. Potter JD: Reconciling the epidemiology, physiology, and molecular biology of colon cancer. JAMA 268 (12): 1573-7, 1992 Sep 23-30. [PUBMED Abstract]

6. Wynder EL, Reddy BS: Dietary fat and fiber and colon cancer. Semin Oncol 10 (3): 264-72, 1983. [PUBMED Abstract]

7. Chen CD, Yen MF, Wang WM, et al.: A case-cohort study for the disease natural history of adenoma-carcinoma and de novo carcinoma and surveillance of colon and rectum after polypectomy: implication for efficacy of colonoscopy. Br J Cancer 88 (12): 1866-73, 2003. [PUBMED Abstract]

Factors With Adequate Evidence of Increased Risk of Colorectal Cancer

Excessive Alcohol Use

There is evidence of an association of colorectal cancer (CRC) with alcoholic beverage consumption. In a meta-analysis of eight cohort studies, the relative risk (RR) for consumption of 45 g/day (i.e., about three standard drinks per day) compared with nondrinkers was 1.41 (95% confidence interval [CI], 1.16–1.72).[1] Case-control studies suggest a modest-to-strong positive relationship between alcohol consumption and large bowel cancers.[2,3] A meta-analysis found that the association did not vary by sex or cancer location within the large bowel.[4]

Five studies have reported a positive association between alcohol intake and colorectal adenomas.[5] A case-control study of diet, genetic factors, and the adenoma-carcinoma sequence was conducted in Burgundy.[6] It separated adenomas smaller than 10.0 mm in diameter from larger adenomas. A positive association between current alcohol intake and adenomas was found to be limited to the larger adenomas, suggesting that alcohol intake could act at the promotional phase of the adenoma-carcinoma sequence.[6]

A large cohort study found a dose-response relationship between alcohol intake and death from CRC, with a RR of 1.2 (95% CI, 1.0–1.5) for four or more drinks per day compared with nondrinkers.[7]

Cigarette Smoking

Most case-control studies of cigarette exposure and adenomas have found an elevated risk for smokers.[8] In addition, a significantly increased risk of adenoma recurrence following polypectomy has been associated with smoking in both men and women.[8] In the Nurses' Health Study, the minimum induction period for cancer appeared to be at least 35 years.[9] Similarly, in the Health Professionals Follow-up Study, a history of smoking was associated with both small and large adenomas and with a long induction period of at least 35 years for CRC.[10] In the Cancer Prevention Study II (CPS II), a large nationwide cohort study, multivariate-adjusted CRC mortality rates were highest among current smokers, intermediate among former smokers, and lowest in nonsmokers, with increased risk observed after 20 or more years of smoking in men and women combined.[11] On the basis of CPS II data, it was estimated that 12% of CRC deaths in the U.S. population in 1997 were attributable to smoking. A large population-based cohort study of Swedish twins found that heavy smoking of 35 or more years' duration was associated with a nearly threefold increased risk of developing colon cancer, although subsite analysis found a statistically significant effect only for rectal cancer, but not colon cancer.[12] Another large population-based case-control study demonstated that current tobacco use and tobacco use within the last 10 years is associated with colon cancer. A

50% increase in risk was associated with smoking more than a pack a day relative to never smoking.[13] However, a 28-year follow-up of 57,000 Finns showed no association between the development of CRC and baseline smoking status, although there was a 57% to 71% increased risk in persistent smokers.[14] No relationship was found between cigarette smoking, even smoking of long duration, and recurrence of adenomas in a population followed for 4 years after initial colonoscopy.[15]

A meta-analysis of 106 observational studies found a RR (ever smokers vs. nonsmokers) for CRC incidence of 1.18 (95% CI, 1.11–1.25), with an absolute risk increase of 10.8 cases per 100,000 person-years (95% CI, 7.9–13.6). There was a statistically significant dose-response effect. In 17 studies with data on CRC mortality, cigarette smoking was associated with CRC death, with a RR (ever smokers vs. never smokers) of 1.25 (95% CI, 1.14–1.37), and an absolute increase in the death rate of 6.0 deaths per 100,000 person-years. For both incidence and mortality, the association was stronger for rectal cancer than for colon cancer.[16]

Obesity

At least three large cohort studies have found an association between obesity and CRC incidence or mortality.[17-19] The Nurses' Health Study found that women with a body mass index (BMI) of more than 29, compared with women with a BMI of less than 21, had an adjusted RR for CRC incidence of 1.45 (95% CI, 1.02–2.07).[17] In the CPS II,[19] men and women with a BMI of 30 to 34.9 had an adjusted RR for CRC mortality (compared with people with a BMI of 18.5–24.9) of 1.47 (95% CI, 1.30–1.66), with a statistically significant dose-response effect.[19] The effects were similar in men and women.

Family/Personal History of Colorectal Cancer and Other Hereditary Conditions

Some of the earliest studies of family history of CRC were those of Utah families that reported a higher number of deaths from CRC (3.9%) among the first-degree relatives of patients who had died from CRC than among sex-matched and age-matched controls (1.2%). This difference has since been replicated in numerous studies that have consistently found that first-degree relatives of affected cases are themselves at a twofold to threefold increased risk of CRC. Despite the various study designs (case-control, cohort), sampling frames, sample sizes, methods of data verification, analytic methods, and countries where the studies originated, the magnitude of risk is consistent.[20-25]

A systematic review and meta-analysis of familial CRC risk was reported.[26] Of 24 studies included in the analysis, all but one reported an increased risk of CRC if there was an affected first-degree relative. The RR for CRC in the pooled study was 2.25 (95% CI, 2.00–2.53) if there was an affected first-degree family member. In 8 of 11 studies, if the index cancer arose in the colon, the risk was slightly higher than if it arose in the rectum. The pooled analysis revealed an RR in relatives of colon and rectal cancer patients of 2.42 (95% CI, 2.20–2.65) and 1.89 (95% CI, 1.62–2.21), respectively. The analysis did not reveal a difference in RR for colon cancer based on location of the tumor (right side vs. left side).[26]

Hereditary CRC has two well-described forms: Familial adenomatous polyposis (including an attenuated form of polyposis), due to germline mutations in the *APC* gene,[27-34] and Lynch syndrome (hereditary nonpolyposis CRC), which is caused by germline mutations in DNA mismatch repair genes.

[35-38] Many other families exhibit aggregation of CRC and/or adenomas, but with no apparent association with an identifiable hereditary syndrome, and are known collectively as familial CRC.[38]

For more information about genetic risk factors for CRC, see Genetics of Colorectal Cancer.

References

1. Cho E, Smith-Warner SA, Ritz J, et al.: Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med 140 (8): 603-13, 2004. [PUBMED Abstract]
2. Newcomb PA, Storer BE, Marcus PM: Cancer of the large bowel in women in relation to alcohol consumption: a case-control study in Wisconsin (United States). Cancer Causes Control 4 (5): 405-11, 1993. [PUBMED Abstract]
3. Meyer F, White E: Alcohol and nutrients in relation to colon cancer in middle-aged adults. Am J Epidemiol 138 (4): 225-36, 1993. [PUBMED Abstract]
4. Longnecker MP, Orza MJ, Adams ME, et al.: A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. Cancer Causes Control 1 (1): 59-68, 1990. [PUBMED Abstract]
5. Boutron MC, Faivre J: Diet and the adenoma-carcinoma sequence. Eur J Cancer Prev 2 (Suppl 2): 95-8, 1993. [PUBMED Abstract]
6. Boutron MC, Faivre J: Alcohol, tobacco and the adenoma-carcinoma sequence: a case-control study in Burgundy, France. [Abstract] Gastroenterology 104 (Suppl 4): A-390, 1993.
7. Thun MJ, Peto R, Lopez AD, et al.: Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 337 (24): 1705-14, 1997. [PUBMED Abstract]
8. Neugut AI, Jacobson JS, DeVivo I: Epidemiology of colorectal adenomatous polyps. Cancer Epidemiol Biomarkers Prev 2 (2): 159-76, 1993 Mar-Apr. [PUBMED Abstract]
9. Giovannucci E, Colditz GA, Stampfer MJ, et al.: A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. J Natl Cancer Inst 86 (3): 192-9, 1994. [PUBMED Abstract]
10. Giovannucci E, Rimm EB, Stampfer MJ, et al.: A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. J Natl Cancer Inst 86 (3): 183-91, 1994. [PUBMED Abstract]
11. Chao A, Thun MJ, Jacobs EJ, et al.: Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. J Natl Cancer Inst 92 (23): 1888-96, 2000. [PUBMED Abstract]
12. Terry P, Ekbom A, Lichtenstein P, et al.: Long-term tobacco smoking and colorectal cancer in a prospective cohort study. Int J Cancer 91 (4): 585-7, 2001. [PUBMED Abstract]
13. Slattery ML, Potter JD, Friedman GD, et al.: Tobacco use and colon cancer. Int J Cancer 70 (3): 259-64, 1997. [PUBMED Abstract]
14. Knekt P, Hakama M, Järvinen R, et al.: Smoking and risk of colorectal cancer. Br J Cancer 78 (1): 136-9, 1998. [PUBMED Abstract]
15. Baron JA, Sandler RS, Haile RW, et al.: Folate intake, alcohol consumption, cigarette smoking, and risk of colorectal adenomas. J Natl Cancer Inst 90 (1): 57-62, 1998. [PUBMED Abstract]
16. Botteri E, Iodice S, Bagnardi V, et al.: Smoking and colorectal cancer: a meta-analysis. JAMA 300 (23): 2765-78, 2008. [PUBMED Abstract]

17. Martínez ME, Giovannucci E, Spiegelman D, et al.: Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 89 (13): 948-55, 1997. [PUBMED Abstract]

18. Giovannucci E, Ascherio A, Rimm EB, et al.: Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 122 (5): 327-34, 1995. [PUBMED Abstract]

19. Calle EE, Rodriguez C, Walker-Thurmond K, et al.: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348 (17): 1625-38, 2003. [PUBMED Abstract]

20. Fuchs CS, Giovannucci EL, Colditz GA, et al.: A prospective study of family history and the risk of colorectal cancer. N Engl J Med 331 (25): 1669-74, 1994. [PUBMED Abstract]

21. Slattery ML, Kerber RA: Family history of cancer and colon cancer risk: the Utah Population Database. J Natl Cancer Inst 86 (21): 1618-26, 1994. [PUBMED Abstract]

22. Negri E, Braga C, La Vecchia C, et al.: Family history of cancer and risk of colorectal cancer in Italy. Br J Cancer 77 (1): 174-9, 1998. [PUBMED Abstract]

23. St John DJ, McDermott FT, Hopper JL, et al.: Cancer risk in relatives of patients with common colorectal cancer. Ann Intern Med 118 (10): 785-90, 1993. [PUBMED Abstract]

24. Duncan JL, Kyle J: Family incidence of carcinoma of the colon and rectum in north-east Scotland. Gut 23 (2): 169-71, 1982. [PUBMED Abstract]

25. Rozen P, Fireman Z, Figer A, et al.: Family history of colorectal cancer as a marker of potential malignancy within a screening program. Cancer 60 (2): 248-54, 1987. [PUBMED Abstract]

26. Johns LE, Houlston RS: A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 96 (10): 2992-3003, 2001. [PUBMED Abstract]

27. Kinzler KW, Nilbert MC, Su LK, et al.: Identification of FAP locus genes from chromosome 5q21. Science 253 (5020): 661-5, 1991. [PUBMED Abstract]

28. Groden J, Thliveris A, Samowitz W, et al.: Identification and characterization of the familial adenomatous polyposis coli gene. Cell 66 (3): 589-600, 1991. [PUBMED Abstract]

29. Leppert M, Burt R, Hughes JP, et al.: Genetic analysis of an inherited predisposition to colon cancer in a family with a variable number of adenomatous polyps. N Engl J Med 322 (13): 904-8, 1990. [PUBMED Abstract]

30. Spirio L, Olschwang S, Groden J, et al.: Alleles of the APC gene: an attenuated form of familial polyposis. Cell 75 (5): 951-7, 1993. [PUBMED Abstract]

31. Brensinger JD, Laken SJ, Luce MC, et al.: Variable phenotype of familial adenomatous polyposis in pedigrees with 3' mutation in the APC gene. Gut 43 (4): 548-52, 1998. [PUBMED Abstract]

32. Soravia C, Berk T, Madlensky L, et al.: Genotype-phenotype correlations in attenuated adenomatous polyposis coli. Am J Hum Genet 62 (6): 1290-301, 1998. [PUBMED Abstract]

33. Pedemonte S, Sciallero S, Gismondi V, et al.: Novel germline APC variants in patients with multiple adenomas. Genes Chromosomes Cancer 22 (4): 257-67, 1998. [PUBMED Abstract]

34. Sieber OM, Lamlum H, Crabtree MD, et al.: Whole-gene APC deletions cause classical familial adenomatous polyposis, but not attenuated polyposis or "multiple" colorectal adenomas. Proc Natl Acad Sci U S A 99 (5): 2954-8, 2002. [PUBMED Abstract]

35. Leach FS, Nicolaides NC, Papadopoulos N, et al.: Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. Cell 75 (6): 1215-25, 1993. [PUBMED Abstract]

36. Papadopoulos N, Nicolaides NC, Wei YF, et al.: Mutation of a mutL homolog in hereditary colon cancer. Science 263 (5153): 1625-9, 1994. [PUBMED Abstract]

37. Nicolaides NC, Papadopoulos N, Liu B, et al.: Mutations of two PMS homologues in hereditary nonpolyposis colon cancer. Nature 371 (6492): 75-80, 1994. [PUBMED Abstract]

38. Miyaki M, Konishi M, Tanaka K, et al.: Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. Nat Genet 17 (3): 271-2, 1997. [PUBMED Abstract]

Factors With Adequate Evidence for a Decreased Risk of Colorectal Cancer

Physical Activity

A sedentary lifestyle has been associated with an increased risk of colorectal cancer in some [1,2] but not all [3] studies. Numerous observational studies have examined the relationship between physical activity and colon cancer risk.[4] Most of these studies have shown an inverse relationship between level of physical activity and colon cancer incidence. The average relative risk (RR) reduction is reportedly 40% to 50%. Large U.S. cohort studies have found statistically significant adjusted RRs of 0.54 (95% confidence interval [CI], 0.33–0.90) [5] and 0.53 (95% CI, 0.32–0.88) [6] when comparing people with high versus low average energy expenditure. A meta-analysis of 52 observational studies found an overall adjusted RR of 0.76 (95% CI, 0.72–0.81), with similar results for men and women.[7]

References

1. White E, Jacobs EJ, Daling JR: Physical activity in relation to colon cancer in middle-aged men and women. Am J Epidemiol 144 (1): 42-50, 1996. [PUBMED Abstract]

2. Slattery ML, Schumacher MC, Smith KR, et al.: Physical activity, diet, and risk of colon cancer in Utah. Am J Epidemiol 128 (5): 989-99, 1988. [PUBMED Abstract]

3. Kune GA, Kune S, Watson LF: Body weight and physical activity as predictors of colorectal cancer risk. Nutr Cancer 13 (1-2): 9-17, 1990. [PUBMED Abstract]

4. Friedenreich CM: Physical activity and cancer prevention: from observational to intervention research. Cancer Epidemiol Biomarkers Prev 10 (4): 287-301, 2001. [PUBMED Abstract]

5. Martínez ME, Giovannucci E, Spiegelman D, et al.: Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 89 (13): 948-55, 1997. [PUBMED Abstract]

6. Giovannucci E, Ascherio A, Rimm EB, et al.: Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 122 (5): 327-34, 1995. [PUBMED Abstract]

7. Wolin KY, Yan Y, Colditz GA, et al.: Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer 100 (4): 611-6, 2009. [PUBMED Abstract]

Interventions With Adequate Evidence for a Decreased Risk of Colorectal Cancer

Aspirin

Evidence from individual participant-level data meta-analyses of randomized controlled trials (RCTs) and observational studies [1,2] investigating the use of aspirin for the prevention of cardiovascular disease indicates that acetylsalicylic acid (ASA) use reduces the incidence of colorectal cancer (CRC), but not until at least 10 years after initiation of therapy (pooled relative risk [RR] of CRC incidence within 10 years of initiation, 0.99 [95% confidence interval (CI), 0.85–1.15] vs. RR, 0.60 [95% CI, 0.47–0.76] at 10–19 years after initiation).[3] In the Women's Health Study, a randomized 2 × 2 factorial trial of 100 mg of ASA every other day for an average of 10 years, CRC incidence was reduced by about 20% after 17.5 years (hazard ratio [HR], 0.80; 95% CI, 0.67–0.97).[4] In a report from the Nurses' Health Study involving 82,911 women followed for 20 years, the multivariate RR for colon cancer was 0.77 (95% CI, 0.67–0.88) among women who regularly used ASA (≥2 standard 325-mg tablets per week) compared with nonregular use. Significant RR was not observed, however, until more than 10 years of use.[5]

The Cancer Prevention Programme (CAPP2), previously known as the Concerted Action Polyposis Prevention project, investigated chemoprevention of CRC in patients with known Lynch syndrome (hereditary nonpolyposis CRC) across 43 international centers. For more information, see the Lynch Syndrome section in Genetics of Colorectal Cancer. Patients were randomly assigned to receive aspirin (600 mg/day), aspirin-placebo, resistant starch (30 g/day), or starch-placebo for up to 4 years. A planned 10-year analysis of CAPP2 data found reduced CRC incidence in patients with Lynch syndrome who took aspirin for at least 2 years when compared with those who took placebo. An intention-to-treat analysis, using Cox proportional hazards regression, showed that aspirin protected against the primary end point of CRC (HR, 0.65; 95% CI, 0.43–0.97; P = .035).[6]

In a randomized study of 635 patients with prior CRC (T1–T2 N0 M0) who had undergone curative resection, ASA intake at 325 mg/day was associated with a decrease in the adjusted RR of any recurrent adenoma as compared with the placebo group (0.65; 95% CI, 0.46–0.91) after a median duration of treatment of 31 months. The likelihood of detection of a new colonic lesion was lower in the ASA group than in the placebo group (HR for the detection of a new polyp, 0.54; 95% CI, 0.43–0.94; P = .022).[7] In a study of 1,121 patients with a recent history of colorectal adenomas, after a mean duration of treatment of 33 months, the unadjusted RRs of any adenoma (as compared with the placebo group) were 0.81 in the 81 mg/day ASA group (95% CI, 0.69–0.96) and 0.96 in the 325 mg/day ASA group (95% CI, 0.81–1.13). For advanced neoplasms (adenomas ≥10.0 mm in diameter or with tubulovillous or villous features, severe dysplasia, or invasive cancer), the RRs were 0.59 (95% CI, 0.38–0.92) in the 81 mg/day ASA group, and 0.83 (95% CI, 0.55–1.23) in the 325 mg/day ASA group, respectively.[8]

ASA has also been evaluated for its potential effects on CRC mortality. A 2010 individual patient level data meta-analysis analyzed long-term (median follow-up, 18.3 years) data from four RCTs of primary and secondary cardiovascular disease prevention; it found that allocation to use of 75 to 1,200 mg of daily ASA for at least one year reduced the cumulative risk of colon cancer death compared with controls (HR, 0.67; 95% CI, 0.52–0.86). Aspirin reduced CRC mortality beginning 10 to 20 years after randomization, but not before.[2] A 2011 individual participant level data meta-analysis examined

data from six RCTs of primary or secondary cardiovascular disease prevention. In trials with allocation to ASA after at least 5 years of in-trial follow-up, the HR for CRC mortality was 0.41 (95% CI, 0.71–1.00). There was no statistically significant effect during the first five years after randomization.[9]

Six RCTs, including five from the United Kingdom, were included in a meta-analysis in which patients were randomly assigned to receive either aspirin or placebo, and the mean scheduled duration of trial treatment was 4 years or more. Individual patient data for all in-trial cancer deaths were obtained. In the three United Kingdom trials, cancer deaths after completion of the trials were obtained via death certification and cancer registration, taking the follow-up to 20 years after randomization. Based on meta-analysis of odds ratios (ORs) from each trial rather than on more sensitive actuarial analysis of the individual patient data, allocation to aspirin in the RCTs reduced the 20-year risk of death due to CRC. ORs for maximum aspirin use were 0.55 for CRC risk (95% CI, 0.41–0.76) and for any aspirin use were 0.58 for CRC risk (95% CI, 0.44–0.78).[10]

The Women's Health Study, the largest randomized trial of aspirin to date (N = 39,876), found no reduction in CRC mortality rates with the use of every other day low-dose aspirin during the first 10 years of follow-up. The study did not report on longer-term risk for CRC mortality.[4]

Aspirin has several important potential harms associated with its use that should be a part of any consideration of its use as a disease prevention strategy. Regular low-dose aspirin use increases the risks for major gastrointestinal bleeding and intracranial bleeding events, including hemorrhagic strokes. A systematic review of studies of aspirin use for primary cardiovascular disease prevention found that use of 100 mg or more of aspirin daily or every other day increased a person’s risk for a major gastrointestinal bleed by 58% (OR, 1.58; 95% CI, 1.29–1.95) or an intracranial hemorrhage by 30% (OR, 1.30; 95% CI, 1.00–1.68). These risks may be greater among older individuals, men, and those individuals with comorbid risk factors that promote a risk of bleeding.[11]

Hormone Therapy (Estrogen Plus Progestin)

Several observational studies have suggested a decreased risk of colon cancer among users of postmenopausal female hormone supplements.[12-15] For rectal cancer, most studies have observed no association or a slightly elevated risk.[16-18]

The Women’s Health Initiative (WHI) trial examined, as a secondary end point, the effect of combined estrogen-plus-progestin therapy and estrogen-only therapy on CRC incidence and mortality. Among women in the combined estrogen-plus-progestin group of the WHI, an extended follow-up (mean, 11.6 years) confirmed that fewer CRC were diagnosed in the combined hormone therapy group than in the placebo group (HR, 0.72; 95% CI, 0.56–0.94); the CRCs in women in the combined group were more likely to have lymph node involvement than the CRCs in women in the placebo group (50.5% vs. 28.6%; $P < .001$) and were classified at higher stages (regional and distant) (68.8% vs. 51.4%; $P = .003$). The number of CRC deaths in the combined group was higher than in the placebo group (37 vs. 27 deaths), but the difference was not statistically significant (HR, 1.29; 95% CI, 0.78–2.11).[19]

Polyp Removal

An analysis of data from the National Polyp Study (NPS), with external, historical controls, has commonly been cited to show a reduction of 76% to 90% in the subsequent incidence of CRC after colonoscopic polypectomy compared with three nonconcurrent, historical control groups.[20] This

study may be biased in several ways that inflate the apparent efficacy of polyp removal; the main problem is that potential enrollees in the NPS were excluded if they had CRC at their baseline examination. Because no such exclusions (or baseline colonoscopy examinations) were done in the three comparison groups, individuals who had CRC at baseline would be counted as having incident CRC in subsequent follow-up. Although adjustments were attempted, it is not possible to know the magnitude of the impact of this problem on the result because it is not known how long CRC may be present without causing symptoms.

An additional long-term follow-up study (median follow-up, 15.8 years; maximum, 23 years) of the NPS cohort suggested an approximately 53% reduction in CRC mortality due to polypectomy (not just exclusion of individuals with CRC at initial exam). However, the degree of reduction must be viewed with caution because this study did not have a direct comparison group, relying mainly on comparison to expected data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. Further, details are not clear regarding factors that may have led to decreased mortality. Patients in the NPS were assigned to colonoscopy at years 1 and 3; colonoscopy was also offered to one of the two comparison groups at year 1; all participants were offered colonoscopy at year 6. However, following year 6, the exact surveillance that patients may have undergone and how that surveillance might have been associated with decreased CRC mortality were not well described. [21]

It is expected that further follow-up in the United Kingdom Flexible Sigmoidoscopy Screening Trial will be able to provide more detail about the long-term effect of polypectomy, at least on the left side of the colon.[21]

Other evidence about the benefit of sigmoidoscopy screening (at which time both polyps and early cancer would be removed) suggests that the impact of endoscopic screening, at least on the left side of the colon, is substantial and prolonged. In an RCT, 170,000 individuals were randomly assigned to one-time sigmoidoscopy versus usual care. At sigmoidoscopy, polyps were removed, cancer was detected, and patients were referred for treatment. Based on sigmoidoscopy findings, individuals were considered to have low risk if they had normal exams or only one or two small (<1 cm) tubular adenomas. These individuals were not referred either for colonoscopy workup, or for colonoscopic surveillance. In a follow-up of 10 years, the left-sided CRC incidence in the low-risk group (about 95% of attendees were low risk) was 0.02% to 0.04% per year—a very low risk of CRC compared with average risk. The cause of reduced risk—whether due to detection and removal of large polyps or small ones, or selection of individuals at lower risk—is yet unclear.[22] The natural history of large polyps is not well known, but some evidence suggests that such lesions become clinical CRC at a rate of approximately 1% per year.[23] As a result of the strong data about the impact of endoscopy on the left colon, evidence from multiple studies has raised questions about the ability of endoscopy to reduce CRC mortality in the right colon.[24-26] Thus, it is unclear what the overall impact of endoscopy (e.g., colonoscopy screening) is, and whether there may be a large difference in impact on the left side of the colon compared with the right side.[24]

Other studies suggest that the polyps with the greatest potential to progress to CRC are larger polyps (i.e., >1.0 cm), which include most of those with villous or high-grade histological features. Retrospective cohort studies also show the harms associated with polypectomy, including bleeding. [27,28]

References

1. Flossmann E, Rothwell PM; British Doctors Aspirin Trial and the UK-TIA Aspirin Trial: Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 369 (9573): 1603-13, 2007. [PUBMED Abstract]
2. Rothwell PM, Wilson M, Elwin CE, et al.: Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 376 (9754): 1741-50, 2010. [PUBMED Abstract]
3. Chubak J, Whitlock EP, Williams SB, et al.: Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force. Ann Intern Med 164 (12): 814-25, 2016. [PUBMED Abstract]
4. Cook NR, Lee IM, Zhang SM, et al.: Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Ann Intern Med 159 (2): 77-85, 2013. [PUBMED Abstract]
5. Wei EK, Colditz GA, Giovannucci EL, et al.: Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the Nurses' Health Study. Am J Epidemiol 170 (7): 863-72, 2009. [PUBMED Abstract]
6. Burn J, Sheth H, Elliott F, et al.: Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet 395 (10240): 1855-1863, 2020. [PUBMED Abstract]
7. Sandler RS, Halabi S, Baron JA, et al.: A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 348 (10): 883-90, 2003. [PUBMED Abstract]
8. Baron JA, Cole BF, Sandler RS, et al.: A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 348 (10): 891-9, 2003. [PUBMED Abstract]
9. Rothwell PM, Fowkes FG, Belch JF, et al.: Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 377 (9759): 31-41, 2011. [PUBMED Abstract]
10. Algra AM, Rothwell PM: Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 13 (5): 518-27, 2012. [PUBMED Abstract]
11. Whitlock EP, Burda BU, Williams SB, et al.: Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med 164 (12): 826-35, 2016. [PUBMED Abstract]
12. Calle EE, Miracle-McMahill HL, Thun MJ, et al.: Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. J Natl Cancer Inst 87 (7): 517-23, 1995. [PUBMED Abstract]
13. Newcomb PA, Storer BE: Postmenopausal hormone use and risk of large-bowel cancer. J Natl Cancer Inst 87 (14): 1067-71, 1995. [PUBMED Abstract]
14. Grodstein F, Newcomb PA, Stampfer MJ: Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 106 (5): 574-82, 1999. [PUBMED Abstract]

15. Terry MB, Neugut AI, Bostick RM, et al.: Risk factors for advanced colorectal adenomas: a pooled analysis. Cancer Epidemiol Biomarkers Prev 11 (7): 622-9, 2002. [PUBMED Abstract]

16. Risch HA, Howe GR: Menopausal hormone use and colorectal cancer in Saskatchewan: a record linkage cohort study. Cancer Epidemiol Biomarkers Prev 4 (1): 21-8, 1995 Jan-Feb. [PUBMED Abstract]

17. Gerhardsson de Verdier M, London S: Reproductive factors, exogenous female hormones, and colorectal cancer by subsite. Cancer Causes Control 3 (4): 355-60, 1992. [PUBMED Abstract]

18. Prihartono N, Palmer JR, Louik C, et al.: A case-control study of use of postmenopausal female hormone supplements in relation to the risk of large bowel cancer. Cancer Epidemiol Biomarkers Prev 9 (4): 443-7, 2000. [PUBMED Abstract]

19. Simon MS, Chlebowski RT, Wactawski-Wende J, et al.: Estrogen plus progestin and colorectal cancer incidence and mortality. J Clin Oncol 30 (32): 3983-90, 2012. [PUBMED Abstract]

20. Winawer SJ, Zauber AG, Ho MN, et al.: Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 329 (27): 1977-81, 1993. [PUBMED Abstract]

21. Zauber AG, Winawer SJ, O'Brien MJ, et al.: Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 366 (8): 687-96, 2012. [PUBMED Abstract]

22. Atkin WS, Edwards R, Kralj-Hans I, et al.: Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 375 (9726): 1624-33, 2010. [PUBMED Abstract]

23. Stryker SJ, Wolff BG, Culp CE, et al.: Natural history of untreated colonic polyps. Gastroenterology 93 (5): 1009-13, 1987. [PUBMED Abstract]

24. Brenner H, Chang-Claude J, Seiler CM, et al.: Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 154 (1): 22-30, 2011. [PUBMED Abstract]

25. Baxter NN, Goldwasser MA, Paszat LF, et al.: Association of colonoscopy and death from colorectal cancer. Ann Intern Med 150 (1): 1-8, 2009. [PUBMED Abstract]

26. Brenner H, Hoffmeister M, Arndt V, et al.: Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst 102 (2): 89-95, 2010. [PUBMED Abstract]

27. Levin TR, Zhao W, Conell C, et al.: Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med 145 (12): 880-6, 2006. [PUBMED Abstract]

28. Warren JL, Klabunde CN, Mariotto AB, et al.: Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 150 (12): 849-57, W152, 2009. [PUBMED Abstract]

Factors With Inadequate Evidence of an Association With Colorectal Cancer

Nonsteroidal Anti-Inflammatory Drugs

One large cohort study (301,240 people with 3,894 colorectal cancer [CRC] cases) found an association between daily or weekly nonaspirin (non-ASA) nonsteroidal anti-inflammatory drug (NSAID) use and reduced 10-year incidence of proximal and distal colon cancer, but not rectal cancer, with a hazard ratio (HR) of 0.67 (95% confidence interval [CI], 0.58–0.77) for daily use for colon cancer. Because exposure to non-ASA NSAIDs was assessed only once, assessment was by self-report, and there is no information on dose or duration of use, the certainty of this single study must be rated low. Further research is needed before this finding can be accepted.[1]

Although evidence is currently inadequate to determine whether NSAIDs reduce CRC incidence, proponents suggest that any effect of these drugs results from their ability to inhibit the activity of cyclooxygenase (COX). COX is important in the transformation of arachidonic acid into prostanoids, prostaglandins, and thromboxane A2. NSAIDs include not only aspirin (ASA, which is considered separately here) and other, first-generation nonselective inhibitors of the two functional isoforms of COX, termed COX-1 and COX-2, but also newer second-generation drugs that inhibit primarily COX-2. Normally, COX-1 is expressed in most tissues and primarily plays a housekeeping role (e.g., gastrointestinal mucosal protection and platelet aggregation). COX-2 activity is crucial in stress responses and in mediating and propagating the pain and inflammation that are characteristic of arthritis.[2]

Nonselective COX inhibitors include indomethacin (Indocin); sulindac (Clinoril); piroxicam (Feldene); diflunisal (Dolobid); ibuprofen (Advil, Motrin); ketoprofen (Orudis); naproxen (Naprosyn); and naproxen sodium (Aleve, Anaprox). Selective COX-2 inhibitors include celecoxib (Celebrex), rofecoxib (Vioxx), and valdecoxib (Bextra). Rofecoxib and valdecoxib are no longer marketed because of an associated increased risk of serious cardiovascular events.

Both celecoxib and rofecoxib have been associated with serious cardiovascular events including dose-related death from cardiovascular causes, myocardial infarction, stroke, or heart failure.[3-6] Four trials that demonstrated this increased risk are summarized in the Table 1. In addition, a network meta-analysis of all large scale randomized controlled trials (RCTs) comparing any NSAID to any other NSAID or placebo found that there is little evidence to suggest that any of the investigated drugs are safe in terms of cardiovascular effects. Naproxen seemed least harmful.[7]

Table 1. Cardiovascular Risks Associated With Celecoxib and Rofecoxib Dose/Drugs

Authors	Dose/Trial Drug	Risk	Study Type
[4]	Rofecoxib <25 mg/qd; rofecoxib >25 mg/qd	OR, 1.47 (0.99–2.17) vs. 3.58 (1.27–10.17)	Nested case-control study all users
[6]	Celecoxib 200 mg/qd vs. 400 mg bid	3.4%; HR, 3.4 (95% CI, 1.4–7.8)	Sporadic adenoma prevention trial (N = 2,035)

bid = twice a day; qd = every day; CI = confidence interval; HR = hazard ratio; OR = odds ratio; RR = relative risk; Rx = prescription.

Authors	Dose/Trial Drug	Risk	Study Type
[5]	Rofecoxib 25 mg/qd	RR, 1.92 (95% CI, 1.19–3.11; *P* = .008)	Chemoprevention of sporadic adenoma
[3]	Rofecoxib 25 mg/qd	RR (estimated), 2.66 (95% CI, 1.03–6.86; *P* = .04)	Chemoprevention of sporadic adenoma; median study Rx 7.4 months

bid = twice a day; qd = every day; CI = confidence interval; HR = hazard ratio; OR = odds ratio; RR = relative risk; Rx = prescription.

Other major harms from all NSAIDs are gastrointestinal bleeding and renal impairment. The incidence of reported major gastrointestinal bleeding events appears to be dose-related.[8]

Celecoxib reduces the incidence of adenomas; however, celecoxib does not have a clinical role in reducing the risk of sporadic CRC. Its long-term efficacy in preventing CRC has not been shown because of increased risk of cardiovascular events, and because there are other effective ways, such as screening to reduce CRC mortality.[9] A population-based retrospective cohort study of nonaspirin NSAID use among individuals aged 65 years and older was associated with lower risk of CRC, particularly with longer durations of use.[10]

Several rigorous studies have demonstrated the effectiveness of sulindac in reducing the size and number of adenomas in familial polyposis.[11,12] In a randomized, double-blind, placebo-controlled study of 77 patients with familial adenomatous polyposis, patients receiving 400 mg of celecoxib twice a day had a 28.0% reduction in the mean number of colorectal adenomas (*P* = .003 for the comparison with placebo) and a 30.7% reduction in the polyp burden (sum of polyp diameters; *P* = .001) as compared with reductions of 4.5% and 4.9%, respectively, in the placebo group. The reductions in the group receiving 100 mg of celecoxib twice a day were 11.9% (*P* = .33 for the comparison with placebo) and 14.6% (*P* = .09), respectively. The incidence of adverse events was similar among the groups.[13]

The NSAID piroxicam, at a dose of 20 mg/day, reduced mean rectal prostaglandin concentration by 50% in individuals with a history of adenomas.[14] Several studies assessing the effect of ASA or other nonsteroidals on polyp recurrence following polypectomy are in progress.[15] In several of these studies, mucosal prostaglandin concentration is being measured.

The potential for use of NSAIDs as a primary prevention measure is being studied. There are, however, several unresolved issues that preclude making general recommendations for their use. These include a paucity of knowledge about the proper dose and duration for these agents, and concern about whether the potential preventive benefits such as a reduction in the frequency or intensity of screening or surveillance could counterbalance long-term risks such as gastrointestinal ulceration and hemorrhagic stroke for the average-risk individual.[16]

Calcium supplements

A randomized placebo-controlled trial tested the effect of calcium supplementation (3 g calcium carbonate daily [1,200 mg elemental calcium]) on the risk of recurrent adenoma.[17] The primary end

point was the proportion of patients (72% of whom were male) in whom at least one adenoma was detected following a first and/or second follow-up endoscopy. A modest decrease in risk was found for both developing at least one recurrent adenoma (adjusted risk ratio [ARR], 0.81; 95% CI, 0.67–0.99) and in the average number of adenomas (ARR, 0.76; 95% CI, 0.60–0.96). The investigators found the effect of calcium was similar across age, sex, and baseline dietary intake categories of calcium, fat, or fiber. The study was limited to individuals with a recent history of colorectal adenomas and could not determine the effect of calcium on risk of the first adenoma, nor was it large enough or of sufficient duration to examine the risk of invasive CRC. After calcium supplementation is stopped, the lower risk may persist up to 5 years.[18] The results of other ongoing adenoma recurrence studies are awaited with interest. It is important to note that the dose of calcium salt administered may be important; the usual daily doses in trials have ranged from 1,250 to 2,000 mg of calcium.

In a randomized, double-blind, placebo-controlled trial involving 36,282 postmenopausal women, the administration of 500 mg of elemental calcium and 200 IU of vitamin D3 twice daily for an average of 7.0 years was not associated with a reduction in invasive CRC (HR, 1.08; 95% CI, 0.86–1.34; $P = .051$). [19] The relatively short duration of follow-up, considering the latency period of CRC of 10 to 15 years, and suboptimal doses of calcium and vitamin D, may account for the negative effects of this trial, although other factors may also be responsible.[20]

Dietary Factors

Dietary fat and meat intake

Colon cancer rates are high in populations with high total fat intakes and are lower in those consuming less fat.[21] On average, fat comprises 40% to 45% of total caloric intake in high-incidence Western countries; in low-risk populations, fat accounts for only 10% of dietary calories.[22] Several case-control studies have explored the association of colon cancer risk with meat or fat consumption, as well as protein and energy intake.[23,24] Although positive associations with meat consumption or with fat intake have been found, the results have been inconsistent.[25] A number of prospective cohort studies have been conducted in the United States and abroad; a systematic review of 13, including the Iowa Women's Health Study and the Nurses' Health Study, concluded that there appeared to be a positive association between meat consumption and CRC incidence. However, the authors noted that because only a few studies tried to investigate the independent effect of meat intake on cancer risk, the observed relationship might be attributed entirely to confounding.[26] Similarly, a 2019 systematic review of observational studies, evaluating the association between processed or unprocessed red meat consumption and CRC incidence and mortality, concluded that a reduction of three servings per week resulted in very small to no decreases in those outcomes, although the certainty around these findings was judged low to very low.[27]

A randomized controlled dietary modification study was undertaken among 48,835 postmenopausal women aged 50 to 79 years who were also enrolled in the WHI. The intervention promoted a goal of reducing total fat intake by 20%, while increasing daily intake of vegetables, fruits, and grains. The intervention group accomplished a reduction of fat intake of approximately 10% more than did the comparison group during the 8.1 years of follow-up. There was no evidence of reduction in invasive CRCs between the intervention and comparison groups with an HR of 1.08 (95% CI, 0.90–1.29).[28] Likewise, there was no benefit of the low-fat diet on all-cancer mortality, overall mortality, or cardiovascular disease.[29] This last observation was echoed in a 2019 systematic review of randomized controlled trials of the effect of variable red meat consumption on cancer outcomes. This

review relied heavily on the WHI to reach the conclusion that there appears to be little to no effect of red meat intake on CRC incidence, although the certainty around this finding is low because of limitations in available studies.[30]

Explanations for the conflicting results regarding whether dietary fat or meat intake affects the risk of CRC [31] include the following:

- Validity of dietary questionnaires used.
- Differences in the average age of the population studied.
- Variations in methods of meat preparation (in some instances, mutagenic and carcinogenic heterocyclic amines could have been released at high temperatures).[32]
- Variability in the consumption of other foods such as vegetables.[33]
- Possible unadjusted bias from differential screening uptake between meat intake groups.

Six case-control studies and two cohort studies have explored potential dietary risk factors for colorectal adenomas.[34,35] Three of the eight studies found that higher fat consumption was associated with increased risk. High fat intake has been found to increase the risk of adenoma recurrence following polypectomy.[36] In a multicenter RCT, a diet low in fat (20% of total calories) and high in fiber, fruits, and vegetables did not reduce the risk of recurrence of colorectal adenomas.[37]

Thus, the evidence is inadequate to determine whether reducing dietary fat and meat would reduce CRC incidence.

References

1. Ruder EH, Laiyemo AO, Graubard BI, et al.: Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort. Am J Gastroenterol 106 (7): 1340-50, 2011. [PUBMED Abstract]
2. Hinz B, Brune K: Cyclooxygenase-2--10 years later. J Pharmacol Exp Ther 300 (2): 367-75, 2002. [PUBMED Abstract]
3. Kerr DJ, Dunn JA, Langman MJ, et al.: Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. N Engl J Med 357 (4): 360-9, 2007. [PUBMED Abstract]
4. Graham DJ, Campen D, Hui R, et al.: Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 365 (9458): 475-81, 2005. [PUBMED Abstract]
5. Bresalier RS, Sandler RS, Quan H, et al.: Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 352 (11): 1092-102, 2005. [PUBMED Abstract]
6. Solomon SD, McMurray JJ, Pfeffer MA, et al.: Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 352 (11): 1071-80, 2005. [PUBMED Abstract]
7. Trelle S, Reichenbach S, Wandel S, et al.: Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 342: c7086, 2011. [PUBMED Abstract]

8. Chan AT, Giovannucci EL, Meyerhardt JA, et al.: Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA 294 (8): 914-23, 2005. [PUBMED Abstract]
9. Arber N, Eagle CJ, Spicak J, et al.: Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 355 (9): 885-95, 2006. [PUBMED Abstract]
10. Smalley W, Ray WA, Daugherty J, et al.: Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. Arch Intern Med 159 (2): 161-6, 1999. [PUBMED Abstract]
11. Labayle D, Fischer D, Vielh P, et al.: Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology 101 (3): 635-9, 1991. [PUBMED Abstract]
12. Giardiello FM, Hamilton SR, Krush AJ, et al.: Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 328 (18): 1313-6, 1993. [PUBMED Abstract]
13. Steinbach G, Lynch PM, Phillips RK, et al.: The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 342 (26): 1946-52, 2000. [PUBMED Abstract]
14. Earnest DL, Hixson LJ, Fennerty MB, et al.: Inhibition of prostaglandin synthesis: potential for chemoprevention of human colon cancer. Cancer Bull 43(6): 561-568, 1991.
15. Vargas PA, Alberts DS: Colon cancer: the quest for prevention. Oncology (Huntingt) 7 (11 Suppl): 33-40, 1993.
16. Imperiale TF: Aspirin and the prevention of colorectal cancer. N Engl J Med 348 (10): 879-80, 2003. [PUBMED Abstract]
17. Baron JA, Beach M, Mandel JS, et al.: Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med 340 (2): 101-7, 1999. [PUBMED Abstract]
18. Grau MV, Baron JA, Sandler RS, et al.: Prolonged effect of calcium supplementation on risk of colorectal adenomas in a randomized trial. J Natl Cancer Inst 99 (2): 129-36, 2007. [PUBMED Abstract]
19. Wactawski-Wende J, Kotchen JM, Anderson GL, et al.: Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med 354 (7): 684-96, 2006. [PUBMED Abstract]
20. Forman MR, Levin B: Calcium plus vitamin D3 supplementation and colorectal cancer in women. N Engl J Med 354 (7): 752-4, 2006. [PUBMED Abstract]
21. Rose DP, Boyar AP, Wynder EL: International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption. Cancer 58 (11): 2363-71, 1986. [PUBMED Abstract]
22. Reddy BS: Dietary fat and its relationship to large bowel cancer. Cancer Res 41 (9 Pt 2): 3700-5, 1981. [PUBMED Abstract]
23. Potter JD: Reconciling the epidemiology, physiology, and molecular biology of colon cancer. JAMA 268 (12): 1573-7, 1992 Sep 23-30. [PUBMED Abstract]
24. Potter JD, McMichael AJ: Diet and cancer of the colon and rectum: a case-control study. J Natl Cancer Inst 76 (4): 557-69, 1986. [PUBMED Abstract]
25. Bingham SA: Diet and large bowel cancer. J R Soc Med 83 (7): 420-2, 1990. [PUBMED Abstract]

26. Hirayama T, Tannenbaum SR, Reddy BS, et al.: A large-scale cohort study on the relationship between diet and selected cancers of the digestive organs. In: Bruce WR, Correa P, Lipkin M, et al., eds.: Gastrointestinal cancer: endogenous factors. Cold Spring Harbor Laboratory, 1981, Branbury Report 7, 409-429.

27. Bjelke E: Epidemiology of colorectal cancer, with emphasis on diet. Int Congr Ser 484: 158-174, 1980.

28. Beresford SA, Johnson KC, Ritenbaugh C, et al.: Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 295 (6): 643-54, 2006. [PUBMED Abstract]

29. Howard BV, Van Horn L, Hsia J, et al.: Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 295 (6): 655-66, 2006. [PUBMED Abstract]

30. Zeraatkar D, Johnston BC, Bartoszko J, et al.: Effect of Lower Versus Higher Red Meat Intake on Cardiometabolic and Cancer Outcomes: A Systematic Review of Randomized Trials. Ann Intern Med 171 (10): 721-731, 2019. [PUBMED Abstract]

31. Goldbohm RA, van den Brandt PA, van 't Veer P, et al.: A prospective cohort study on the relation between meat consumption and the risk of colon cancer. Cancer Res 54 (3): 718-23, 1994. [PUBMED Abstract]

32. Sugimura T: Carcinogenicity of mutagenic heterocyclic amines formed during the cooking process. Mutat Res 150 (1-2): 33-41, 1985 Jun-Jul. [PUBMED Abstract]

33. Lee HP, Gourley L, Duffy SW, et al.: Colorectal cancer and diet in an Asian population--a case-control study among Singapore Chinese. Int J Cancer 43 (6): 1007-16, 1989. [PUBMED Abstract]

34. Neugut AI, Jacobson JS, DeVivo I: Epidemiology of colorectal adenomatous polyps. Cancer Epidemiol Biomarkers Prev 2 (2): 159-76, 1993 Mar-Apr. [PUBMED Abstract]

35. Kampman E, Giovannucci E, van 't Veer P, et al.: Calcium, vitamin D, dairy foods, and the occurrence of colorectal adenomas among men and women in two prospective studies. Am J Epidemiol 139 (1): 16-29, 1994. [PUBMED Abstract]

36. Neugut AI, Garbowski GC, Lee WC, et al.: Dietary risk factors for the incidence and recurrence of colorectal adenomatous polyps. A case-control study. Ann Intern Med 118 (2): 91-5, 1993. [PUBMED Abstract]

37. Schatzkin A, Lanza E, Corle D, et al.: Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med 342 (16): 1149-55, 2000. [PUBMED Abstract]

Factors and Interventions With Adequate Evidence of no Association With Colorectal Cancer

Estrogen-Only Therapy

The estrogen-only intervention component of the Women’s Health Initiative was conducted among women who had a hysterectomy, with colorectal cancer (CRC) incidence included as a secondary trial

end point. CRC incidence was not decreased among women who had taken estrogens. After a median follow-up of 7.1 years, 58 invasive cancers occurred in the estrogen arm compared with 53 invasive cancers in the placebo arm (hazard ratio [HR], 1.12; 95% confidence interval [CI], 0.77–1.63). Tumor stage and grade were similar in the two groups; deaths after CRC were 34% in the hormone group compared with 30% in the placebo group (HR, 1.34; 95% CI, 0.58–3.19).[1]

Statins

Overall, evidence indicates that statin use neither increases nor decreases the incidence or mortality of CRC. Although some case-control studies have shown a reduction in risk, neither a large cohort study [2] nor a meta-analysis of four randomized controlled trials [3] found any effect of statin use.

References

1. Ritenbaugh C, Stanford JL, Wu L, et al.: Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. Cancer Epidemiol Biomarkers Prev 17 (10): 2609-18, 2008. [PUBMED Abstract]
2. Jacobs EJ, Rodriguez C, Brady KA, et al.: Cholesterol-lowering drugs and colorectal cancer incidence in a large United States cohort. J Natl Cancer Inst 98 (1): 69-72, 2006. [PUBMED Abstract]
3. Dale KM, Coleman CI, Henyan NN, et al.: Statins and cancer risk: a meta-analysis. JAMA 295 (1): 74-80, 2006. [PUBMED Abstract]

Latest Updates to This Summary (04/11/2025)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Incidence and Mortality

Updated statistic with estimated new cases and deaths for 2025 (cited Bray et al. as reference 1 and American Cancer Society as reference 2). Also revised text to state that between 2012 and 2021, incidence rates increased by 2.4% per year in individuals younger than 50 years and by 0.4% per year in individuals aged 50 to 64 years.

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