Updates on Translational Research on Prevention of Polyps and Colorectal Cancer

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Abstract

Morbidity and mortality from colorectal cancer (CRC) can be effectively reduced through early detection and prevention. To date, strategies for managing CRC risk have focused primarily on secondary prevention, through screening asymptomatic individuals for colorectal neoplasia. In the United States, implementation of screening among individuals age ≥ 50 has led to not only decreased CRC-related mortality but also reduced CRC incidence through colonoscopic removal of precancerous polyps. In contrast to screening's endpoint of early detection, the goal of primary prevention of CRC is to arrest and/or reverse colorectal carcinogenesis. Observational studies and randomized clinical trials continue to examine effects of specific pharmacologic agents (chemoprevention) and dietary interventions on development of advanced colorectal neoplasia. This review will present an overview of strategies for primary and secondary prevention of CRC, including endoscopic, pharmacologic, and dietary interventions.

Keywords

- primary prevention
- colorectal cancer
- chemoprevention
- colonoscopy

Each year approximately 134,000 individuals are diagnosed with colorectal cancer (CRC) in the United States, and 49,000 die as a result of the disease.¹ Fortunately, in recent years the absolute numbers of CRC diagnoses and deaths have been declining, in large part due to widespread implementation of colorectal screening. The United States Preventive Services Task Force (USPSTF) has given a Grade A recommendation supporting screening average-risk individuals for CRC beginning at age 50 years (earlier for individuals at above-average risk) and recognizes the effectiveness of several different screening modalities for early detection of malignant and premalignant colorectal neoplasms (► **Table 1**).¹ Emerging data suggest that additional pharmacologic and dietary interventions may have a role in primary prevention of colorectal carcinogenesis.

Screening for Colorectal Neoplasia = Secondary Prevention

The value of screening in reducing morbidity and mortality from CRC has been recognized for more than 25 years. Studies of fecal occult blood testing (FOBT) demonstrated that early detection of CRC was associated with reduction in

disease-specific mortality and the landmark National Polyp Study proposed that the vast majority of CRCs could be prevented through use of colonoscopy with polypectomy.² However, despite consensus on the benefit of CRC screening, recent U.S. data suggest that one-third or more of eligible individuals do not participate in CRC screening.³ The USPSTF, along with other professional society guidelines, have endorsed several different strategies for CRC screening, which are categorized broadly into stool-based tests and direct visualization tests (► **Table 1**).

Stool-Based Tests

Stool-based tests for occult gastrointestinal bleeding, including guaiac fecal occult blood (gFOBT, Hemoccult) and fecal immunochemical (FIT) tests, are noninvasive and relatively inexpensive (30–100 U.S. dollars [USD]), and are currently employed as first-line tests for CRC screening in many European countries. The Minnesota Colon Cancer Control study randomized nearly 50,000 subjects to usual care versus annual/biennial gFOBT testing and found after 30 years of follow-up significantly reduced CRC-related mortality among individuals randomized to gFOBT (relative risk [RR]: 0.68;

Table 1 USPSTP-recommended tests for screening for CRC

Test	Patient population	Exam interval	Sensitivity CRC colorectal adenomas
Stool-based tests	Average risk		
Guaiac Fecal Occult Blood Test	Average risk	Q1 y	CRC 37–79%
Fecal immunochemical test	Average risk	Q 1 y	CRC 73–88% Advanced adenomas 22–40%
Fecal immunochemical DNA test	Average risk	Q 1–3 y	CRC 92% Advanced adenomas 42%
Direct visualization tests			
Colonoscopy	Average, moderate, and high risk	Q 1–10 y, depending on risk strata	Reference standard ^a
CT colonography	Average risk	Q 5 y	CRC >90% Adenomas (>6 mm) 67–98%
Flexible sigmoidoscopy (+/– FIT)	Average	Q 5–10 y	N/A due to incomplete colon visualization

Abbreviation: CRC, colorectal cancer.

Source: Adapted from Lin et al.⁵

^aReports from tandem colonoscopy studies suggest adenoma miss rate of 25%.¹⁰

95% confidence interval [CI]: 0.56–0.82).⁴ Technological improvements have increased the sensitivity and specificity of FIT for detection of adenocarcinomas; however, the sensitivity for detecting premalignant colorectal neoplasms (adenomas, sessile serrated polyps, flat dysplasia) remains suboptimal, ranging from 22 to 40% for advanced adenomas.⁵

Fecal DNA testing (FIT-DNA) has recently been included among the USPSTF-endorsed tests. The Cologuard (Exact Sciences) stool DNA test contains molecular assays for aberrantly methylated *BMP3* and *NDRG4* promoter regions, mutant *KRAS*, and β -actin, as well as an immunochemical assay for human hemoglobin and has higher sensitivity compared with other stool-based tests (92% for cancers and 42% for advanced precancerous lesions).⁶ FIT-DNA's significantly higher cost (>500 USD) and the requirement for colonoscopy to follow up an abnormal result are limitations to its cost-effectiveness relative to other CRC screening modalities.

Direct Visualization Tests

Colonoscopy

Colonoscopy is considered the “gold standard” colorectal screening test and is currently the most commonly used modality for CRC screening in the United States. Colonoscopy is the only test recommended for screening and surveillance for individuals whose CRC risk is above average. In observational cohorts, prior colonoscopy has been associated with significant reductions in CRC incidence, as well as mortality (hazard ratio [HR]: 0.57, 95% CI: 0.45–0.72, compared with no screening).⁷ The vast majority of CRCs are believed to develop from polyps, and since colorectal adenomas are found in $\geq 20\%$ of individuals undergoing screening colonoscopy, use of colonoscopy as the initial screening test pro-

vides an opportunity to combine diagnostic and therapeutic interventions into a single test. The fact that colonoscopy is an invasive procedure, requires a full bowel preparation, and is associated with a not-insignificant complication rate (perforation and major bleeding reported in 4–8/10,000)⁵ limits its appeal for many patients; furthermore, the fact that colonoscopy is the most costly of all the CRC screening tests has economic implications.

Although it is common practice to use colonoscopy as the reference standard against which other CRC screening tests are compared, there is growing recognition that colonoscopy does not offer perfect protection. There has been attention on the problem of “interval cancers,” defined as CRC diagnosed in a patient who has undergone one or more previous colonoscopy exams. Although the estimates from the National Polyp Study suggested that colonoscopy would reduce CRC-related mortality by more than 90%,² recent case-control and observational studies have found the actual reduction in CRC mortality to be considerably lower (50–60%),^{8,9} with colonoscopy providing significantly less protection from cancers originating in the proximal colon. Based on studies which have documented colonoscopy miss rates for adenomas of 25%,¹⁰ the predominant theory is that the majority of these interval cancers develop from lesions not identified during standard colonoscopy. In addition to emphasizing high-quality endoscopic technique and optimizing bowel preparation, use of technologies which enhance mucosal visualization (e.g., narrow band imaging, chromoendoscopy, wide-view endoscopes) may offer opportunities to improve visualization of neoplastic precursors whose location and/or morphology make them likely to be missed by conventional white-light endoscopy.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy has been studied in several randomized clinical trials and has proven effective in reducing CRC-specific mortality compared with no screening (RR: 0.73, 95% CI: 0.66–0.82).^{5,11} However, the fact that these exams visualize less than 50% of the mucosal surface of the colon and that the mortality benefit is limited to neoplasms in the distal colon are major limitations for this invasive test. Although, flexible sigmoidoscopy is used commonly for screening in European countries, it is rarely used for first-line CRC screening in the United States, as it has ranked below colonoscopy in preference among both physicians and patients.

Computed Tomographic Colonography

Computed tomographic (CT) colonography uses radiographic two- or three-dimensional computerized reconstructions for detection of colonic neoplasms. In expert centers, CT colonography has demonstrated excellent sensitivity for detection of CRC (>90%) comparable to that of conventional colonoscopy^{12,13}; however, reports suggest that performance characteristics in community settings may be more variable. Sensitivity of CT colonography for detecting adenomas is considerably lower (68–90%) and polyps less than 6 mm are often not reported.^{5,14} Like colonoscopy, high-quality CT colonography exams usually require a bowel preparation; however, recent studies have examined stool-tagging as a means to avoid bowel cleansing.¹⁵ Potential risks associated with repeated radiation exposure and uncertainties regarding sensitivity for flat neoplasms, surveillance interval, and costs related to follow-up of incidental findings (identified in up to 27–69% of screened subjects)⁵ had been viewed as limitations for widespread implementation of CT colonography for CRC screening. Even so, the recently revised USPSTF CRC screening guidelines now include CT colonography among its approved tests.¹

Novel Strategies for Early Detection of Colorectal Neoplasia

Colorectal cancers are broadly classified into three categories on the basis of their molecular characteristics: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP).¹⁶ The molecular mechanisms of pathogenesis of colorectal neoplasms have implications not only for disease prognosis and treatment response but also for approaches to early detection. The search for noninvasive biomarker tests with performance characteristics that exceed those of current stool-based tests continues. In addition to the U.S. Food and Drug Administration (FDA)-approved FIT-DNA stool-based test, the performance of other stool DNA markers, methylated vimentin, and noncoding microRNAs (miRNAs) are currently under investigation. Although stool-based CRC screening tests are widely used, adherence remains suboptimal, highlighting the need for blood-based tests with good sensitivity and specificity, which may promote increased uptake of CRC screening.

The FDA recently approved methylated *Septin 9* (*SEPT9*) gene as a blood-based CRC screening test.¹⁷ Methylated *SEPT9* was identified among potential candidate markers in paired stool and blood samples from CRC patients. While initial case-control studies reported high (90%) sensitivity for CRC, a prospective trial screening peripheral blood of asymptomatic individuals for methylated *SEPT9* found that sensitivity and specificity were lower (73 and 81%, respectively), with positive predicted value of 5%. Furthermore, there was significant variation in test characteristics by disease stage, with sensitivity for stage 1 cancers of only 36%,¹⁸ suggesting there continues to be a need for convenient CRC screening tests capable of detecting early-stage disease.¹⁷

Novel Approaches for Preventing Colorectal Neoplasia

CRC risk stratification: How do we identify patients most likely to benefit from risk reduction interventions?

The average individual in the United States has a lifetime risk of CRC of approximately 5% and CRC screening of average-risk individuals aged 50 to 75 years has been recommended by the USPSTF (Grade A recommendation).¹ Most diagnoses of CRC are made in individuals with no family history of CRC who would be classified as average risk; however, it is important to recognize that there are individuals whose CRC risk is significantly higher than average, and these patients are potential candidates for early screening and/or risk reduction interventions. Family history remains one of the strongest risk factors for CRC and risk stratification algorithms rely on family history (in addition to personal history of colorectal neoplasia and/or inflammatory bowel disease) to categorize individuals as average, moderate, or high risk.¹⁹ Hereditary cancer syndromes, associated with germline mutations in highly penetrant cancer genes, are implicated in 3 to 5% of CRC cases²⁰ and the National Comprehensive Cancer Network (NCCN) has published guidelines to facilitate identification of individuals for whom referral for genetic risk assessment for CRC should be considered²¹ (►Table 2).

Approaches to CRC risk assessment, which integrate personal and family history, along with molecular characteristics of colorectal neoplasms, provide opportunities to identify individuals with genetic predisposition to CRC. Although there have been several clinical algorithms and risk models developed to risk stratify patients and identify individuals at risk for Lynch's syndrome, the most common hereditary CRC syndrome (e.g., PREMM1, 2, 6, MMRpro),^{22,23} the sensitivity and specificity of these remains imperfect. Although recommendations for CRC screening for all individuals age ≥50 years has resulted in overall reductions of CRC-related incidence and mortality, CRC incidence among young individuals younger than 50 years continues to rise by 1.5% per year for reasons which remain unclear.²⁴ Investigation of potential genetic and/or environmental factors that impact risk for colorectal neoplasia is critical, as presymptomatic identification of individuals at increased risk for CRC would provide opportunities for early intervention, including enhanced screening and/or chemoprevention (►Table 3).

Table 2 NCCN criteria for referral for genetic risk evaluation for high-risk syndromes associated with CRC^a

1. Individuals meeting the Revised Bethesda Guidelines
2. Individuals meeting the Amsterdam Criteria
3. Individuals with >20 colorectal adenomas
4. Individuals with multiple gastrointestinal hamartomatous polyps or serrated polyposis
5. Individuals from a family with a known hereditary syndrome associated with CRC with or without a known mutation
6. Individuals with desmoid tumor, cribriform morular variant of papillary thyroid cancer, or hepatoblastoma

Abbreviation: CRC, colorectal cancer.

^aNCCN Clinical Practice Guidelines in Oncology Version 2.2015, nccn.org.²¹

Primary Prevention of Colorectal Neoplasia: Diet, Health Behaviors, and Drugs

From a clinical perspective, most interventions to reduce morbidity and mortality from CRC have focused on screening and early detection, which are classified as secondary prevention approaches. Primary prevention presupposes that there are interventions which can be implemented to effectively arrest and/or reverse colorectal neoplasia. The dysregulation of cellular processes, which lead to tumor development, is usually preceded by genetic and/or epigenetic alterations, which can be inherited or sporadic. These genomic disruptions may occur simply by chance, or as a consequence of acute or chronic processes such as inflammation, toxic exposures, injury, and/or aging.

While several observational studies have demonstrated trends suggesting association between various health behaviors, lifestyle, and dietary factors on CRC incidence and mortality, the data supporting associations have not been conclusive, in large part due to the inability to separate the effects of individual exposures. Geographic variations in CRC incidence support the theory that a portion of CRC risk could be related to components of the Western diet, which tends to be high fat, low fiber, and rich in red meat. Heterocyclic amines, nitro compounds, and aromatic polycyclic carbonates which form in charred/well-done meat have been associated with carcinogenesis in experimental models, and meta-analyses of cohort studies have observed associations between increased intake of red meat and processed meat with increased CRC incidence (RR: 1.28, 95% CI: 1.15–1.42).²⁵ Although intake of fruits and vegetables has been assumed to be protective against colorectal neoplasia, data have been mixed with meta-analysis of several cohort studies demonstrating no significant reduction in overall risk, but possible trend for reduction in distal CRC.²⁶

Polyphenolic compounds, found in many types of berries, are antioxidants, which may have protective effects against colorectal neoplasia through suppression of inflammation, oxidative stress, proliferation, and angiogenesis, and preliminary in vivo and in vitro studies have shown promise.²⁷ Curcumin, derived from the turmeric plant, has been used for centuries for medicinal purposes and appears to have antioxidant properties inhibiting growth of cancer cells through inhibition of DNA methyltransferases and histone acetyltransferase, suggesting alterations in DNA methylation are a potential mechanism for CRC chemoprevention.²⁸ While nutritional and lifestyle changes hold promise for CRC risk reduction, the logistical challenges of conducting large randomized-controlled trials (RCTs) which require adherence to strict behavioral and dietary interventions for long time periods remain formidable. Based on the assumption that it is easier to take a pill than to change diet and/or health behaviors, there continues to be significant interest in testing the potential chemopreventive properties of a variety of other dietary and pharmacologic supplements.

Agents for CRC Chemoprevention

Chemoprevention, defined as use of agents that induce biological mechanisms to prevent carcinogenesis, has been touted as one of the most promising strategies for primary prevention of CRC. An important guiding principle for implementing primary prevention is that the intervention must be well tolerated and that benefits to the patient must outweigh any risks that may result from the intervention. Several case-control studies, cohort studies, and RCTs have examined the effects of different agents on various endpoints related to prevention of colorectal neoplasia, including CRC-related mortality, CRC incidence, as well as recurrence of colorectal polyps/adenomas. The use of colorectal polyps as surrogate endpoints for CRC prevention has

Table 3 Effect of chemoprevention agents for risk reduction of colorectal neoplasia

Intervention	CRC incidence	Adenoma recurrence
Aspirin	OR = 0.71, (95% CI = 0.66–0.77) ³²	RR: 0.83 (95% CI: 0.72–0.96) ³⁶
Calcium		RR: 0.80 (95% CI: 0.68–0.93) ⁵⁶
COX-2 inhibitor (Celecoxib)		RR: 0.55 (95% CI: 0.48–0.64) ⁴¹
Metformin		RR: 0.60 (95% CI: 0.39–0.92) ⁴⁹

Abbreviations: CI, confidence interval; OR, odds ratio.

been a matter of debate, but has been justified based on the assumption that adenomatous polyps are the precursors to most CRCs and that prevention of adenomas would be expected to translate into prevention of CRC. Furthermore, because the timeframe for adenoma development is shorter and incidence is higher compared with CRC, using adenoma reduction/prevention as an endpoint for chemoprevention studies requires shorter observation time and smaller sample sizes.²⁹

Aspirin

Aspirin is the agent with the strongest data supporting an association between use and reduction of CRC-related morbidity and mortality, as well as prevention of recurrence of colorectal adenomas. While the exact mechanism of action for aspirin's effectiveness against colorectal neoplasia remains a topic for debate, leading theories include its effects on prostaglandin synthesis, modulation of inflammatory responses, and Wnt/Beta-catenin signaling.³⁰ Several case-control studies have found significant associations between use of aspirin and overall and disease-specific survival in CRC patients (specifically those whose tumors have somatic mutations in *PIK3CA*),³¹ and RCTs examining the effect of aspirin use on survival in CRC patients are currently underway. With regard to CRC prevention, case-control and cohort studies have demonstrated reduced CRC incidence among regular aspirin users (pooled analysis of 10 studies; odds ratio [OR] = 0.71, 95% CI: 0.66–0.77)³² and long-term follow-up of a RCT conducted in subjects in the Women's Health Study found similar reduction in CRC incidence among women randomized to aspirin (HR: 0.80; 95% CI: 0.67–0.97).³³ A protective effect of aspirin for the prevention of colorectal adenomas has also been documented in several RCTs,^{34,35} with meta-analysis confirming significantly reduced risk for adenomas (RR: 0.83, 95% CI: 0.72–0.96).³⁶ Nevertheless, it is important to recognize that chronic aspirin use is not without risk, and severe adverse events including major gastrointestinal and intracranial bleeding have been reported (increase of 0.29 and 0.1 events per 1,000 person-years, respectively).³⁰ Doses of aspirin used vary by clinical trial, ranging from 81 to 600 mg daily, and the optimal dose for prevention of colorectal neoplasia is yet to be determined. Consequently, before recommending aspirin for chemoprevention of colorectal neoplasia, it is recommended that clinicians consider risks versus benefits based on each patient's personal history. Nevertheless, recognizing the significant benefit of aspirin for preventing mortality in patients at increased risk for cardiovascular disease, the USPSTF in 2016 endorsed aspirin use for primary prevention of both cardiovascular disease and CRC for individuals aged 50 to 69 years whose 10-year cardiovascular disease risk is greater than 10%.³⁷

Nonsteroidal Anti-inflammatories

Like aspirin, the exact mechanisms by which nonsteroidal anti-inflammatory drugs (NSAIDs) prevent colorectal neoplasia remain unclear, but are presumed to involve prostaglandin synthesis, modulation of inflammation, and Wnt-

signaling. Sulindac, a nonselective NSAID, has been used for decades for the control of duodenal and rectal polyps in patients with familial adenomatous polyposis (FAP).³⁸ Although FAP patients commonly demonstrate an initial response with measurable reductions in polyp burden, this is often not sustained and reports of invasive CRCs arising in FAP patients treated with sulindac have raised concerns that neoplastic progression may continue even while polyp number and size are observed to decrease.³⁹ Sulindac has been used in combination with other agents in clinical chemoprevention trials (see discussion on eflornithine and erlotinib later).

Cyclooxygenase 2 (COX-2), an enzymatic mediator of acute and chronic inflammation, is overexpressed in many colorectal neoplasms and has been identified as a potential target for chemoprevention. Pharmacologic agents which selectively inhibited COX-2 initially generated significant enthusiasm because they offered the potential benefits associated with nonselective NSAIDs while minimizing gastrointestinal toxicities resulting from COX-1 inhibition. There have been several RCTs, which have tested various COX-2 inhibitors for the prevention of colorectal neoplasia. In patients with FAP, use of high-dose celecoxib (400 mg twice daily) was associated with a 28% reduction in polyp number.⁴⁰ RCTs conducted in patients with a history of sporadic adenomas also found that COX-2 inhibitor use was associated with significant reduction in adenoma incidence (RR: 0.55; 95% CI: 0.48–0.64, for celecoxib⁴¹ and RR: 0.76; 95% CI: 0.69–0.83 for rofecoxib).⁴² However, occurrence of serious adverse events, including significant increases in severe cardiovascular complications, raised alarms about the risk/benefit profile of specific NSAIDs. After discussions with the FDA over safety, the manufacturers of rofecoxib removed the drug from the market, and the indication for use of other COX-2 inhibitors for purposes of cancer chemoprevention has since been withdrawn.

Difluoromethylornithine/Eflornithine

Difluoromethylornithine (DFMO) is an inhibitor of ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine synthesis.⁴³ ODC is a target of the *c-MYC* oncogene and has been linked to malignant transformation of epithelial cells. Treatment of APC^{Min/+} mice with DFMO and sulindac demonstrated decreased polyamine contents in the intestine and decreased tumors.⁴³ A phase III double-blind RCT in patients with a history of sporadic adenomas found that treatment with DFMO/eflornithine (500 mg) plus sulindac (150 mg once a day) was associated with a 70% reduction in adenoma recurrence.⁴⁴ A large international Phase III RCT of eflornithine plus sulindac in FAP patients is currently underway. At high doses, DFMO has been associated with hearing loss, which can be reversed with stopping the drug.

Erlotinib

Erlotinib is a small molecule inhibitor of epidermal growth factor receptor (EGFR) currently used for treatment of patients with non-small cell lung cancers that lack activating *KRAS* mutations and patients with advanced pancreatic

cancer (in combination with gemcitabine). EGFR is overexpressed in most CRCs and anti-EGFR monoclonal antibodies such as panitumumab and cetuximab have proven effective in the treatment of KRAS wild-type CRCs. As EGFR signaling promotes COX-2 expression, investigators are exploring the hypothesis that treatment with EGFR inhibitors might be effective for prevention of colorectal neoplasia. Animal studies have demonstrated the effectiveness of EGFR inhibitors in reducing intestinal polyp burden in APC^{Min/+} mice.⁴⁵ A recent double-blind RCT which randomized patients with FAP to treatment with sulindac and erlotinib versus placebo found the erlotinib/sulindac combination to be effective in reducing duodenal polyp burden.⁴⁶ It is worth noting that grade 1 and 2 adverse events (mostly rash and mucositis) were reported by more than 80% of subjects in the treatment arm which in many cases required dose reduction. Plans are underway for additional studies to determine optimal dose needed to achieve effectiveness while minimizing side effects.

Metformin

Epidemiological studies have found increased incidence for cancers of various types among individuals with type 2 diabetes. The biological mechanisms underlying the association between diabetes and cancer risk have not been definitively determined; however, the role of high insulin levels on cancer risk is being actively investigated. Metformin is a biguanide derivative that suppresses gluconeogenesis and glycogenolysis and increases glucose uptake without stimulating insulin secretion. Studies have demonstrated that administration of metformin reduced intestinal neoplasms in APC^{Min/+} mice⁴⁷ and suppressed formation of aberrant crypt foci in human subjects.⁴⁸ A recent phase 3 RCT conducted by investigators in Japan randomized 151 nondiabetic patients with a previous history of resected adenomatous polyps to treatment with metformin 250 mg daily versus placebo. After 1 year of treatment, patients in the metformin treatment arm had significantly fewer adenomas compared with those who received placebo (RR: 0.60, 95% CI: 0.39–0.92).⁴⁹ It is worth noting that study subjects were selected for enrollment on the basis of history of multiple high-risk and/or advanced adenomas; consequently, larger studies will be needed to demonstrate whether the findings are generalizable.

Vitamin D and Calcium

Vitamin D has been shown in vitro to inhibit angiogenesis and cell proliferation and promote differentiation and apoptosis of epithelial cells.⁵⁰ Epidemiological studies have found associations between vitamin D deficiency and increased risk for CRC and colorectal adenomas.⁵¹ Increased calcium intake has been shown to reduce development of large bowel tumors in animal models, possibly through reducing epithelial hyperproliferation induced by bile and fatty acids and/or suppression of induction of the tumor promotion enzyme ODC.⁵² Clinical trials of calcium supplementation in human subjects at average and increased risk for CRC have also demonstrated reduced incidence of colorectal adenomas.^{53,54}

Given the potential synergy between calcium and vitamin D, a recent RCT with 2 × 2 factorial design examined the effect of daily supplementation with vitamin D (1,000 IU) and/or calcium (1,200 mg) over 3 to 5 years. After 3 to 5 years of follow-up of 2,259 randomized subjects with prior history of colorectal adenomas, investigators found no significant reduction in adenoma recurrence.⁵⁵ Proposed explanations for the lack of effect included the relatively short timeframe. Nevertheless, a meta-analysis of three placebo-controlled RCTs found that calcium supplementation was associated with a significant reduction in recurrence of colorectal adenomas (RR: 0.80, 95% CI: 0.68–0.93)⁵⁶ with magnitude of effect similar to that observed with aspirin use.

Other Vitamins

In contrast to calcium and vitamin D where the preventive effect on colorectal neoplasia has been reproducible, data to support significant benefits of other vitamins, including antioxidants such as vitamin A, C, and E, and B vitamins, are lacking. The Polyp Prevention Study randomized patients to β-carotene, vitamin E, or vitamin C either alone or in combination and failed to demonstrate an effect on the primary endpoint of adenoma recurrence,⁵⁷ and meta-analysis of cohort studies also found no protective effect for antioxidants.⁵⁸ With regard to supplementation with folic acid, results of a large RCT demonstrated no protection, and instead suggested a trend toward possible increase in risk for colorectal adenomas.⁵⁹

Omega 3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in oily fish and are involved in phospholipid membranes, cellular signaling, and lipid metabolism. There is robust literature documenting cardiovascular benefits of omega 3 PUFAs, and epidemiological studies have found an association between increased intake and a decrease in CRC risk.⁶⁰ In vitro studies have shown that omega 3 PUFAs have antitumor effects through regulation of apoptosis, antiangiogenic and anti-inflammatory effects, reducing COX-2 expression, and prostaglandin E2 production.⁶¹ Animal studies have demonstrated that omega 3 PUFAs reduce intestinal polyp burden in APC^{Min/+} mice. Human studies conducted in individuals with FAP have also demonstrated reduction in adenoma burden.⁶² A recent analysis of data from the Nurses' Health Study and Health Professionals Follow-up Study demonstrated an association between high omega 3 PUFA intake and decreased risk for CRC, specifically for subtypes of tumors with mismatch repair deficiency, suggesting a possible effect on T-cell regulation enhancing the immune response against cancer.⁶³ RCTs are underway to examine the effects of omega 3 PUFAs on the endpoints of mucosal biomarkers, adenoma incidence, and CRC mortality.

Summary

Morbidity and mortality from CRC can be effectively reduced through primary and secondary prevention. Population-

based screening for CRC is cost-effective, and choice of CRC screening test depends on the individuals' risk status. The search for noninvasive biomarker tests with high sensitivity and specificity for colorectal neoplasia continues. Interventions that combine chemoprevention with endoscopic polypectomy will inform strategic approaches to CRC risk reduction for individuals at average and above average risk for colorectal neoplasia.

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