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Harvard Report on Cancer Prevention

Volume 3: Prevention of colon cancer in the United States

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Introduction

Colon cancer is a preventable disease. We understand many aspects of its pathogenesis and the factors that influence its development. In addition, several effective screening tools exist for the early detection of colon cancer. However, to date, we have not effectively utilized existing knowledge to reduce the burden of colon cancer in the United States. Colon cancer is the third most common form of cancer among men and women in the United States [1]. When statistics for men and women are combined, colon cancer is second only to lung cancer as the leading cause of cancer mortality in the United States, accounting for 47,700 deaths each year [1]. In this article, we review the pathogenesis of this disease and the burden it presents to the United States. We then review modifiable risk factors for colon cancer and summarize the evidence for screening as a preventive measure. Finally, we discuss preventive strategies for reducing the burden of colon cancer in the United States. This article will focus exclusively on colon cancer, rather than colon and rectal cancers combined, since rectal cancers make up a small portion of overall cancers, the risk factors for colon and rectal cancers differ, and the benefits of screening for rectal cancer alone are minimal.

1. Burden of colon cancer in the United States

For the average American man or woman, lifetime risk of colon cancer is approximately 6% or 1 in 18 [2]. As shown in Figure 1, incidence of colon cancer rises sharply after age 35, with 90% of disease occurring in individuals over age 50 [2]. At all ages, incidence is slightly higher among men than women.

Incidence rates have recently begun to decline after increasing for several decades. Between 1973 and 1985, the age-standardized incidence of colon cancer rose from 32 to 38 cases per 100,000. Since 1985, however, incidence has declined by nearly 20%, with 31 cases diagnosed per 100,000 individuals in 1995 [2]. These trends most likely reflect the earlier detection and increased removal of premalignant polyps.

As a result of reduced incidence and improved diagnostic tools and treatment, mortality and survival rates have also improved in the last two decades. In 1973, there were 22 colorectal cancer deaths per 100,000 individuals, and colon cancer patients had a 50% chance of surviving for five years [2]. In 1995, the mortality rate for colon cancer declined to 17 per 100,000, and 5-year survival rates rose to 63% [2]. The decline in mortality due to colon cancer has been more marked among women (27%) than men (15%), although the improvement in survival rates has been similar [2].

Survival rates depend largely on stage at diagnosis (see Table 1). Nearly 94% of patients diagnosed with localized colon cancer survive beyond five years, compared to 70% of those diagnosed with regional disease, and 9% of those whose cancers are metastatic at diagnosis [2]. Despite evidence that early detection of colon cancer improves survival, only 35% of all colon cancer patients are being diagnosed when their disease is most treatable [2]. Nearly 38% are not diagnosed until their colon cancer has progressed to regional disease, and 22% are diagnosed when the cancer has already metastasized. The average patient dying of colorectal cancer in the United States will lose over 13 years of life [3].

A disproportionate amount of the colon cancer burden falls within the black population, where both incidence and mortality rates are higher than among whites. In 1995 there were 31 incident cases of colon cancer per 100,000 whites and 38 per 100,000 blacks [2]. In addition, although the overall population has seen a significant decline in colon cancer incidence and mortality in the past 20 years, rates of both disease and death have actually increased among blacks. Incidence rates were 18% higher in 1995 than in 1973, and mortality rates increased 9% during the same time period [2]. Differences in mortality and survival between blacks and whites may be explained partially by differences in stage at diagnosis. Blacks are less likely to be diagnosed with localized disease and more likely to be diagnosed with late-stage colon cancer than whites [2].

2. Natural history of colon cancer

Pathogenesis

Much is known about the pathogenesis of colon cancer. Colonic cells accumulate alterations in the genes that

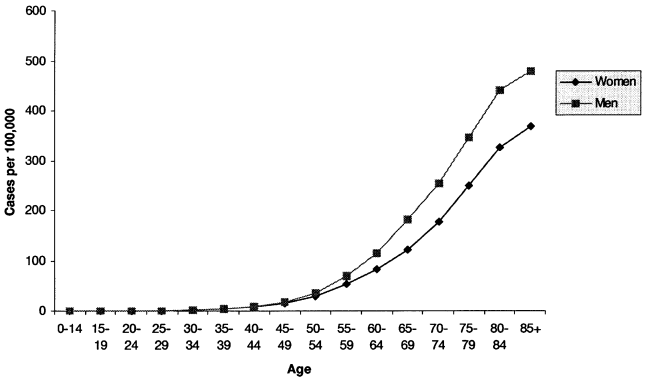


Fig. 1. Incidence of colon cancer by age among men and women (from Ries *et al.* [2]).

Table 1. Stage distribution of colon cancer diagnosed in the United States and 5-year survival rates, 1989–1994 (from Ries *et al.* [2])

Stage at diagnosis	5-Year survival rate	% of cases
Localized	94	35
Regional	69	38
Distant	9	22
Unstaged	30	5

control cell growth and differentiation, particularly tumor suppressor genes and proto-oncogenes. Although this process appears to depend on the overall accumulation of alterations, rather than a specific sequence, [4] several events have been identified as occurring early or late in the multistage process. For example, the mutation or loss of the APC gene (a tumor suppressor gene), the mutation of K-ras (a proto-oncogene), and the loss of DNA methylation occur early in the pathway, while loss of p53 (a tumor-suppressor gene) occurs later [4]. As a result of genetic alterations, benign adenomatous polyps arise in the colonic epithelium and some of these, if left undetected, may transform through a stage of dysplasia into carcinoma [5].

Although there are many types of colonic polyps, only adenomatous polyps have the potential to develop into invasive cancer. Adenomatous polyps are the most common type of polyp; they are found in approximately 25% of people by age 50, and prevalence increases with age [5]. However, few adenomatous polyps will progress to carcinoma within a person's lifetime [5, 6]. While only 6% of adults develop colon cancer, in autopsy studies, 10–33% have colonic polyps at death [6]. Of the adenomatous polyps that do progress into invasive cancer within a person's lifetime, the transformation appears to take 10–15 years on average [5, 6].

Although there is limited direct evidence for the proposed adenoma–carcinoma sequence, the indirect evidence is abundant [5]. The average age of onset of adenomatous polyps precedes that of carcinoma by several years [7], and few cancers arise in the absence of polyps [8]. Patients who have had at least one large polyp (> 1 cm across the diameter) and patients who have familial adenomatous polyposis are at increased risk of colon cancer [8–10], and most of the subsequent cancers arise at the site of large polyps that were left in place [8]. Many carcinomas contain remnants of adenomatous polyps [11–13], and adenomatous polyps and carcinomas share many genetic changes. In populations where screening programs are in place and adenomatous polyps are detected early and removed, rates of colon cancer decline [14, 15]. Finally, adenomatous polyps and carcinomas share a similar set of risk factors.

Familial clustering

At least two familial syndromes predispose individuals to colon cancer: familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Inherited mutations in mismatch repair genes and the APC gene are responsible for increased colon cancer risk in individuals affected by these syndromes [16]. FAP is rare, occurring in about 1 per 5,000 individuals [17] and accounting for less than 1% of all colon cancers nationwide [9]. It is characterized by the presence of hundreds to thousands of adenomatous polyps that develop within the first several decades of life. Affected individuals have an almost 100% risk of developing colon cancer by their forties [5]. HNPCC is more common than FAP and may account for 2% of colon cancers [18]. In individuals affected with either of these syndromes, colon cancer will be expressed 15–20 years earlier than in unaffected individuals [5, 17]. In addition, patients with FAP or HNPCC are at increased risk of other cancers [17]; FAP is associated with increased risk of adenomas and carcinomas in the stomach and proximal small intestine, and HNPCC with cancers of the endometrium, ovary, and gastrointestinal, urinary and biliary tracts.

Familial clustering of colon cancer also occurs in the absence of a defined genetic syndrome. This may be due to genetics or to shared lifestyle and dietary factors within families. Individuals whose parents, siblings, or children have been diagnosed with colorectal cancer or adenomatous polyps are nearly twice as likely to develop colon cancer as those without a family history [5, 19]. The effect of family history appears to be greatest among those under age 45 and among those who have two or more affected first-degree relatives [20].

Inflammatory bowel disease

Compared to the general population, patients with inflammatory bowel disease (IBD) are at substantially greater risk of developing colon cancer [5]. Risk of colon cancer increases with duration of IBD, although most cancers do not occur until after 8 years of pancolitis [5]. Because of the high risk of colon cancer associated with IBD, affected patients should be under increased surveillance for colon cancer [5].

3. Primary prevention

Overview

Complementing the knowledge of colon cancer biology is an understanding of the risk factors that influence both the development and prevention of this disease. Almost 75% of all colon cancer cases occur in people with none of the known predisposing factors discussed above (genetic syndromes, family history, and personal history of IBD or colon cancer) [20]. Therefore, it is important to focus attention on behavioral factors that are associated with reduced risk of colon cancer. The extended timeframe of the adenoma–carcinoma sequence provides an excellent window of opportunity to intervene on risk factors and prevent the development of malignancy. In this section, we summarize the evidence for the modifiable factors related to colon cancer. Some of the factors may influence polyp development, while others may influence progression to malignancy. The factors are discussed in the order of their potential impact on colon cancer, with consideration given to the positive and negative effects of each factor on other health outcomes.

Physical activity

Lack of physical activity is the risk factor most consistently shown to be associated with an increased risk of colon cancer. Among both men and women, high levels of physical activity may decrease risk of colon cancer by as much as 50% [21]. Although studies have not consistently used a standard measure of physical activity or defined exactly what constitutes a 'high' level of activity, dose-response relationship between activity and colon cancer has been consistently observed across various study designs and populations [22–27]. Physical activity also appears to reduce risk of large adenomatous polyps, which suggests that it may act early in the adenoma–carcinoma sequence [26, 28, 29].

Maintaining high levels of physical activity throughout life appears to impart the greatest protection [30, 31]. In the Harvard Alumni Study, men who were at least moderately active at two assessments were 48% less likely to develop colon cancer than men who were inactive at both assessments [32]. However, this does not mean that those who have been sedentary in the past cannot reap the benefits if they become active. The same study showed that among men who were sedentary at the initial assessment, those who increased their activity during the 11–15 year follow-up period were 13% less likely to develop colon cancer than those who remained sedentary during that time period [32]. In addition, the level of activity needed to reduce colon cancer risk appears moderate. Data from the prospective Nurses' Health Study and Health Professionals Follow-Up Study indicate that both men and women can lower their risk of colon cancer simply by engaging in moderate physical activity [26, 27], such as brisk walking or stair climbing.

Several mechanisms have been proposed for the relationship between physical activity and colon cancer. Physical activity may decrease gastrointestinal transit time, thereby minimizing contact with potential carcinogens in the stool [33]. It may also reduce circulating levels of insulin, which is a growth factor for colonic epithelial cells and may promote tumor growth [34, 35]. Additional hypotheses suggest that physical activity alters prostaglandin levels, improves immune function, and modifies bile acid metabolism [27].

Red meat

There is considerable evidence that high intake of red meat increases risk of colon cancer among both men and women. Three of seven cohort studies and 16 of 26 case-control studies have reported a positive association between red meat and colon cancer [36]. For most studies showing an association, the median relative risk between the high and low categories of red meat intake is about 2, with most falling between 1.5 and 2.5 [37]. In the Nurses' Health Study, women who consumed beef, lamb, or pork as a main dish at least once a day were two and a-half times more likely to be diagnosed with colon cancer than women who consumed meat as a main dish less than once a month [38]. Similarly, in the Health Professionals Follow-Up Study, men who consumed beef, pork, or lamb as a main dish at least 5 times a week had a relative risk of 3.6 compared to men who ate meat less than once a month [39].

Several mechanisms have been proposed to explain the relationship between red meat and colon cancer. First, the specific fatty acid content of red meat may be

particularly harmful [40]. However, the fatty acids in beef are not unique and overlap substantially with dairy fat, which has not been shown to be related to colon cancer. Second, fat from red meat may be less readily digested or absorbed in the small intestine than fat from other sources; therefore, more of it may reach the large bowel [41]. Third, initiators or promoters may be formed when red meat is cooked, particularly at high temperatures [42, 43]. Finally, high consumption of red meat may increase concentrations of fecal iron, which could influence risk of colon cancer via the generation of hydroxyl radicals [41].

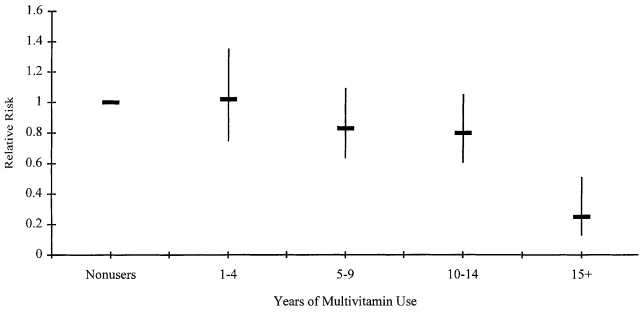


Fig. 2. Relative risk for colon cancer by years of multivitamin use (from Giovannucci *et al.* [45]).

Multivitamins containing folic acid

Although numerous studies have demonstrated an inverse association between colon cancer and intake of vegetables containing folate [36], recent evidence suggests that use of multivitamins containing folic acid may be more beneficial in reducing colon cancer risk than dietary intake of folate [44, 45]. In a population-based case-control study, risk of colon cancer was halved among men and women who reported daily multivitamin use, compared to those who never used multivitamins [44]. In the Nurses' Health Study, women who used multivitamins for at least 15 years were 75% less likely to develop colon cancer than women who never took multivitamins [45] (see Figure 2). Women whose diets were high in folate but who never took multivitamins had no significant reduction in risk.

The differential protection of folate depending on its source may be due to the higher dose and bioavailability of the folic acid found in multivitamins. The dose of folic acid contained in multivitamins (0.4 mg) is much greater than the daily dietary intake of folate for most individuals [46], and folic acid in multivitamins is more bioavailable than folate in vegetables [46]. Although foods that are naturally high in folate may provide additional benefits from other micronutrients, consumption of these foods is probably less effective than multivitamin use in enhancing folic acid status and reducing colon cancer risk [45].

The mechanisms by which multivitamins containing folic acid may reduce colon cancer risk are not well-established. High intake of folate has been associated with lower risk of colorectal adenomas, suggesting that folate may be protective at the polyp formation stage [45]. On the molecular level, chronic folate deficiency may lead to abnormalities in DNA synthesis or repair [45]. It may also contribute to aberrations in DNA methylation, which may contribute to carcinogenesis, possibly by influencing both the activation of oncogenes and the inactivation of tumor suppressor genes [47]. Low folate levels in combination with low methionine and high alcohol may be particularly deleterious, because alcohol reduces the availability of folic acid. In the Health Professionals Follow-Up Study, men who had a low-methyl diet (low methionine and folate and high alcohol) were more than three times as likely to develop colon cancer as men who had a high-methyl diet [47]. Although epidemiologic data, animal studies, and molecular studies, indicating an association between polypmorphisms in a gene involved in folate metabolism and risk of colon cancer, suggest that folic acid is the key protective nutrient in multivitamins, vitamin D intake may also protect against colon cancer [48]. Given the substantially lower risk seen among those taking a multivitamin containing folic acid, the preventive recommendation is to take a daily multivitamin containing 0.4 mg of folic acid.

Obesity

Obesity appears to influence the development of adenomatous polyps, as well as the progression of polyps to malignancy. Both men and women with excess body weight are at increased risk of polyps and colon cancer; however, the magnitude of increased risk may be slightly higher among men than women [36]. In two recent cohort studies, a 50% increase in colon cancer risk was seen among obese women [27], compared to an 80% increase in risk among obese men [26]. Men with high levels of abdominal fat appear to be at particularly high risk [26].

The underlying mechanism for the relationship between obesity and colon cancer is unknown. However, it has been hypothesized that elevated insulin or other growth-related factors may be mediating the influence of obesity [35]. Abdominal obesity, in particular, is a strong determinant of hyperinsulemia, a condition which may promote colonic tumor growth.

Vegetables, fruit, and fiber

High intake of vegetables may offer moderate protection against colon cancer, although most available evidence for this association is from case-control studies, which are susceptible to reporting bias [36, 49]. Evidence for a protective association is stronger for women than men [36, 49]. In one cohort study of over 760,000 adults, Thun *et al*. compared risk of fatal colon cancer among those in the highest quintile of vegetable intake and those in the lowest quintile [50]. The relative risk was 0.6 for women in the highest quintile (95% CI: 0.5–0.9) and 0.8 for men in the highest quintile (95% CI: 0.6–1.0). In another prospective study, raw vegetables, green leafy vegetables, and cruciferous vegetables appeared to be particularly protective for both men and women [51]. However, the relation of overall fruit and vegetable consumption to risk of colon cancer was weak and not significant.

Which of the potentially anticarcinogenic agents contained in vegetables is responsible for the possible protective effect of vegetables is not presently clear. While many studies have focused on fiber as the protective agent in vegetables, recent evidence suggests the protection conveyed by vegetables may not be attributed to fiber [52]. Among the case-control and cohort studies that have examined dietary sources of fiber separately, intake of fruits and vegetables was protective against colon cancer, whereas grain fiber and cereal intake were either unrelated or positively associated with colon cancer risk [52]. Steinmetz and Potter have suggested that vegetables contain an 'anticarcinogenic cocktail' of substances, including both recognized nutrients and nonnutritive constituents, which inhibit the formation of carcinogens, act as substrates for endogenous production of anticarcinogens, reduce the capacity of transformed cells to proliferate, act as antioxidants, and fine-tune inducible enzyme systems to handle occasional high intakes of carcinogens [53]. Increased vegetable consumption may also increase stool bulk and decrease transit time, thereby minimizing contact between the colon and potential carcinogens in the stool [53].

Alcohol and tobacco use

Alcohol and tobacco use may increase risk of colon cancer. Although not entirely consistent, the majority of studies support an association between alcohol intake and increased risk of colon cancer among both men and women [41]. Moreover, alcohol is related to increased risk of colorectal adenomas [29, 54]. A dose–response relationship has been observed across several studies [36], and some evidence suggests that even moderate drinkers who consume 1 drink a day are at higher risk of colon cancer than nondrinkers [36]. The effects of alcohol appear to be exacerbated by low levels of folate and methionine. In the Health Professionals Follow-Up Study, increased risk of colon cancer was observed among both current and past drinkers, but only among those with low intakes of methionine or folate [47]. Because alcohol is an antagonist of methyl-group metabolism, it may imbalance DNA methylation, which may then contribute to carcinogenesis.

Cumulative exposure to cigarette smoking may increase risk of colon cancer, as well as colon polyps, among both men and women [55]. Both the Nurses' Health Study and the Health Professionals Follow-Up Study demonstrated significant elevations in risk among smokers who had been smoking for at least 35 years [56, 57]. In a 26-year follow-up study of U.S. veterans, a 40% increase in colon cancer risk was observed among individuals who had begun smoking before age 15, and a 10% increase was observed for those who began smoking after age 25 [58]. The long latency period between initiation of smoking and elevation in risk, coupled with the consistent relationship seen between smoking and colorectal adenomas, suggests that tobacco is an initiator of colorectal carcinogenesis [55]. However, not all studies are consistent. A recent 20-year follow-up study of Swedish men found no association between cigarette smoking and colon cancer, even among those who had smoked for 30 years or more [59].

In summary, daily consumption of alcohol and long-term exposure to cigarette smoke appear to increase risk of colon cancer. Although tobacco has received widespread attention due to its causal relationship with lung cancer and a variety of other diseases, alcohol has not received this attention from the cancer prevention community, despite its causal relation with upper aerodigestive cancers. Because alcohol consumption presents such a wide variety of health-related effects, including a substantial reduction in coronary heart disease, personal decisions are complex but effects on cancer risk should be considered.

Aspirin and other non-steroidal anti-inflammatory agents

Regular aspirin use over an extended period may reduce risk of colon cancer by as much as 50% among both men and women. Although 'regular aspirin use' is not defined consistently across epidemiologic studies, and there is still considerable debate as to the dose and duration required to convey protection, evidence suggests that taking one tablet at least every other day for a minimum of 10 years will reduce colon cancer risk; weaker and conflicting data support a benefit with less

than 10 years of use [60]. In one study, a 70% reduction in colon cancer incidence was observed among individuals using aspirin for 10 or more years, and a weaker association was observed for use for less than 10 years [61]. In the Nurses' Health Study, the association between consistent aspirin use (2 or more tablets a week) and colon cancer risk also varied with duration of use [62]. No reduction in risk was observed for the first 9 years of aspirin use, a weak but nonsignificant reduction was seen for 10–19 years of use, and a 44% lower risk was observed among women who took aspirin regularly for at least 20 years. Aspirin use may also be related to polyp occurrence [29]. Because of the competing risks and benefits of aspirin with respect to cardiovascular disease and gastrointestinal irritation and bleeding, the public health implications of recommending widespread use of aspirin for colon cancer prevention must be weighed carefully.

The mechanism by which aspirin influences colon cancer risk is not yet well understood. Aspirin may indirectly inhibit prostaglandins (eicosanoids that influence tumor growth) by acting as a potent, irreversible inhibitor of cyclooxygenase-2, an enzyme necessary for the synthesis of prostaglandins. Alternatively, aspirin may inhibit phospholipase activity, which is important in various aspects of intracellular signaling [60].

Hormone use

Use of postmenopausal hormones may reduce a woman's risk of colon cancer [63]. A recent meta-analysis suggested a 20% reduction in colon cancer risk for postmenopausal women who had ever taken postmenopausal hormone therapy compared to those who never used hormones [63]. The most striking reduction in risk was among current hormone users, whose risk was reduced by 44% compared to never users. It is not yet clear whether extended duration of use conveys additional protection. Data from the Cancer Prevention Study II suggest a significant trend of decreasing risk with increasing duration of use [64], while data from the Nurses' Health Study indicate no additional protection from extended duration of use [65].

Evidence supporting an association between oral contraceptives and colon cancer is less consistent. The majority of studies examining the association have reported a reduction in risk among oral contraceptive users [66–71], but results have typically not been statistically significant [66–70]. The Nurses' Health Study is the only prospective study to demonstrate a significant relationship between oral contraceptive use and colon cancer risk; women who used oral contraceptives for at least eight years were 40% less likely to develop colon cancer than women who never used oral contraceptives [71].

Exogenous estrogens may influence colon cancer risk by suppressing bile acid production [72]. Bile acids are hypothesized to initiate or promote malignant change in the colonic epithelium. Exogenous estrogens may also influence risk of colon cancer by altering DNA methylation [73]. Finally, estrogen decreases serum levels of insulin-like growth factor I, an important mitogen which may be associated with colon cancer [63].

Although use of exogenous hormones may reduce risk of colon cancer, a reduction in risk must be weighed against other risks and benefits of estrogen use. For example, postmenopausal hormone use is also associated with decreased risk of coronary disease and fractures and increased risk of breast cancer [74], while oral contraceptive use is protective against endometrial and ovarian cancer [75–77].

Summary of primary prevention of colon cancer

If Americans were to modify the behavioral factors discussed above at an early enough age to reverse risk, more than 50% of colon cancers could be prevented in the long term [78]. Table 2 summarizes the relative risk, as well as the prevalence, of each of the modifiable factors. The factors are rank-ordered based on the strength of the scientific evidence that a particular factor affects colon cancer risk and on the presence or absence of health benefits or adverse health effects that might result from the factor. For example, the observational data on physical activity and colon cancer are very consistent, the benefits of physical activity for cardiovascular and bone health are well-established, and the adverse consequences of physical activity are minimal if it is done sensibly. The observational data on red meat consumption and colon cancer are less consistent, there may be cardiovascular benefits to restricting red meat consumption, and the adverse consequences are almost entirely cultural and economic. For multivitamins, the observational data that prolonged usage prevents colon cancer are consistent with the biology of carcinogenesis, the cardiovascular benefits of multivitamin use are well-established, and there are no known substantial adverse effects. For aspirin, it is now clear that eicosanoids play a role in neoplasia. However, there is no certain knowledge about dose and regimen, and the side effects of gastrointestinal and cerebral bleeding would become worrisome if large numbers of healthy people were to begin taking aspirin for prolonged periods.

Notably, the majority of the population is not engaging in the behaviors known to be most protective against colon cancer: 80% of adults are active less than

Table 2. Relative risks and prevalence of modifiable and non-modifiable factors related to colon cancer

	Relative risk	% of US population exposed	
		Women	Men
Lifestyle factors			
Physical activity (≥3 hours of leisure-time activity per week vs. none)	0.6	19% [79]	22% [79]
Red meat (≥7 servings per week vs. < 1 serving/month)	1.5	25%	25%
Multivitamin use (≥15 years vs. never)	0.5	22% [80]	17% [80]
Obesity (BMI ≥27 vs. < 21)	1.5	34% [95]	32% [95]
Vegetables and fruit (≥5 servings/day vs. < 3 servings/day)	0.7	23% [96]	18% [96]
Alcohol (≥4 drinks/week vs. none)	1.4	24% [95]	46% [95]
Cigarette use (current vs. never)	1.5	23% [97]	27% [97]
Aspirin use (≥15 years vs. never)	0.7	13% [98]	11% [98]
Estrogen replacement (≥5 years vs. never)	0.8	7% [99, 100]	NA
Oral contraceptive use (≥5 years vs. never)	0.7	20% [99]	NA
Screening			
Fecal occult blood test (in past year vs. never)	0.7	29% [101]	34% [101]
Flexible sigmoidoscopy (in past 5 years vs. never)	0.5	24% [101]	33% [101]
Non-modifiable factors			
Family history (sibling or parent with colorectal cancer)	1.8	5% [100, 102]	5% [100,102]
Inflammatory bowel disease (diagnosed ≥10 years)	1.5	0.1% [103]	0.1% [103]

3 hours a week [79] and 25% consume more than 7 servings of meat a week. In addition, 80% do not take a daily multivitamin [80], which is a relatively inexpensive and simple way to reduce risk. Given that most Americans are not engaging in behaviors known to prevent development of malignancy, early detection of polyps and colon cancer must become routine and commonplace. In the next section, we discuss the evidence for screening as a preventive measure.

4. Screening

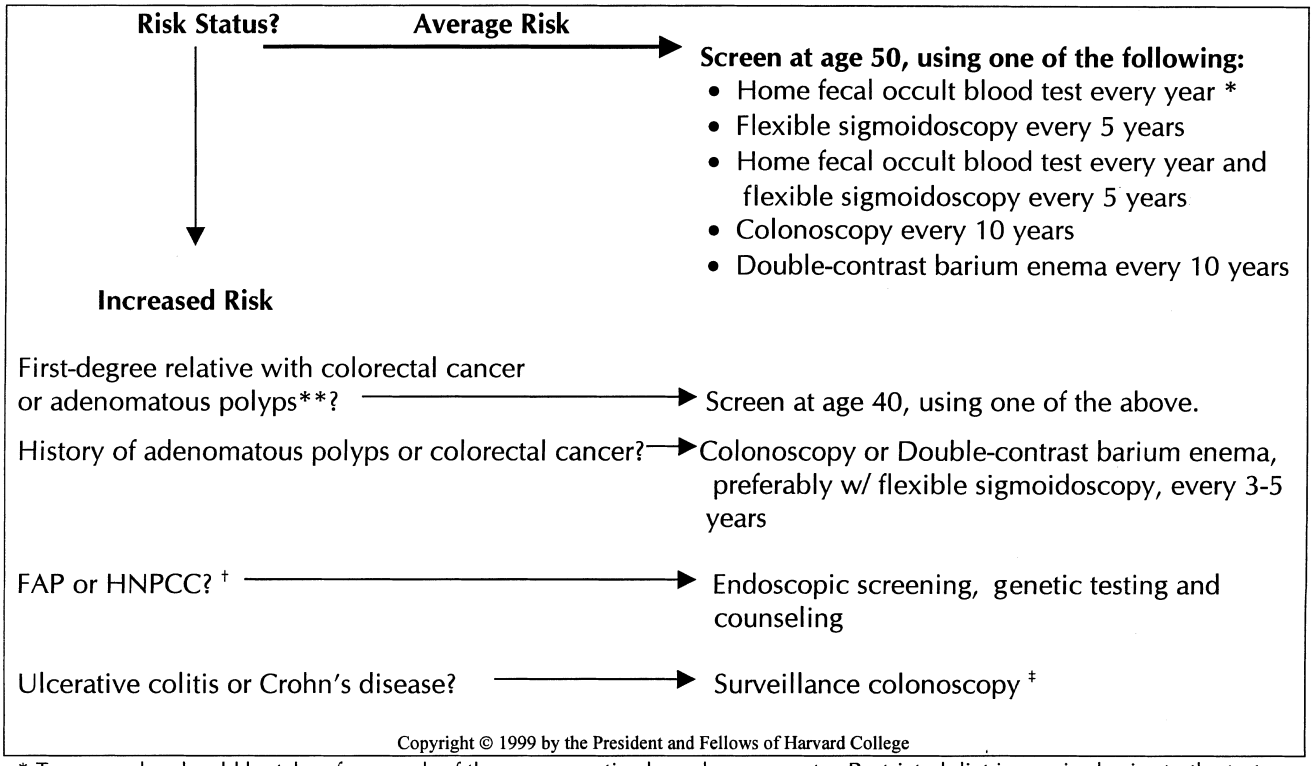
For most diseases, screening is considered 'secondary prevention' because it detects early forms of cancer, but does not prevent the actual development of disease. However, colon cancer screening can be considered either primary prevention or secondary prevention because the tests have the ability to detect – and often remove – both precancerous polyps and carcinomas. Primary prevention via screening involves the removal of precancerous polyps that may have progressed to carcinoma if left undetected. Evidence suggests that removal of polyps in a population does lead to a reduction in the incidence of colon cancer [14]. Secondary prevention, on the other hand, involves detecting carcinoma at the earliest, most treatable stage of disease. This type of prevention will not reduce colon cancer incidence, but will reduce mortality rates.

A variety of screening tests are effective in detecting adenomatous polyps and carcinomas, including fecal occult blood tests, flexible sigmoidoscopy, colonoscopy, and double-contrast barium enema. Screening by any one of these methods is recommended for all asymptomatic patients over age 50 [5]. Those who have a family history of colon cancer, a genetic syndrome, or a personal history of inflammatory bowel disease should be screened at an earlier age and perhaps more frequently [5]. (See Figure 3 for a detailed screening algorithm for colon cancer.) Below we summarize the evidence for fecal blood tests and flexible sigmoidoscopy, the two colon cancer screening tests currently recommended by the US Preventive Services Task Force [6]. Although colonoscopy and barium enema are also effective tests for early detection of polyps and carcinomas [5], data are still limited on their use in population-based screening programs.

Fecal occult blood test

Fecal occult blood testing (FOBT) is based on the premise that precancerous polyps and carcinomas will bleed more than normal mucosa [5]. It involves smearing stool on a slide impregnated with guaiac, adding hydrogen peroxide, and looking for a change in color [81]. Two stool samples are typically taken from each of three consecutive bowel movements, and if one of these six samples is positive, the FOBT is considered positive. A positive FOBT should lead to full examination of the colon via colonoscopy or barium enema.

Ingestion of particular foods and anti-inflammatory agents can lead to false-positives, as can nonneoplastic conditions that cause gastrointestinal bleeding, such as hemorrhoids and peptic ulcers. Rehydration of stool samples, typically done to improve the sensitivity of FOBT, will also increase the rate of false-positives [6, 81]. For asymptomatic patients over age 50, the reported positive predictive value (PPV) of FOBT is 20–30% for



* Two samples should be taken from each of three consecutive bowel movements. Restricted diet is required prior to the test.
** Applies only if relative was diagnosed with adenomatous polyps before age 60.
† Familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer.
‡ After 8 years of pancolitis or 15 years of left-sided disease.

Fig. 3. Screening for colorectal cancer in asymptomatic men and women.

adenomas and 2–11% for carcinomas [6]. The low PPV has important implications in terms of the cost of the screening program and the discomfort associated with follow-up procedures.

Despite its low positive predictive value, FOBT has demonstrated effectiveness in reducing colon cancer mortality. A recent meta-analysis of four randomized controlled trials showed that screening by FOBT reduced colon cancer mortality by 16%, on average, among those allocated to annual FOBT screening, and by 23% among those who were actually screened [82]. Individual trials suggested a greater reduction in mortality associated with annual screening and rehydrated slides (33%) [83] than with biennial screening and nonrehydrated slides (14–18%) [84, 85]. These results support the recommendation by the US Preventive Services Task Force for annual, rather than less frequent, screening by FOBT [6].

Flexible sigmoidoscopy

Unlike FOBT, flexible sigmoidoscopy serves as both a screening and diagnostic tool. It allows for direct examination of the colon, and any polyps detected can be biopsied and removed during the procedure. Thus, flexible sigmoidoscopy can reduce both colon cancer incidence and mortality.

Flexible sigmoidoscopy involves the insertion of a flexible fiberoptic sigmoidoscope into the colon. There are two lengths of flexible sigmoidoscopes, 35 and 60 cm. Both have 85% sensitivity within the region they can visualize, but the longer instrument can view a greater portion of the colon and therefore detect a larger proportion of lesions [81]. The 35 cm instrument can view 50–75% of the sigmoid colon [6], although only 30–40% of all adenomatous polyps will arise in the region reached by this instrument [86]. The 60 cm instrument can reach the splenic flexure, visualizing the distal one-third of the colon, where about 40–60% of all polyps and carcinomas will arise [5].

Recent evidence suggests that individuals screened by sigmoidoscopy are less likely to develop colon cancer [87] and less likely to die of colon cancer than individuals not screened [87–90]. Early evidence was based on screening with a rigid sigmoidoscope, and there were limited data on lifestyle factors that might have con-

founded the relationship between screening and mortality [88, 90]. The most compelling evidence to date comes from a recent prospective cohort study of nearly 25,000 men ages 40–75 for whom screening history and a wide range of lifestyle factors were available [87]. Investigators found that flexible sigmoidoscopy was associated with a 42% reduction in colon cancer incidence and a 50% reduction in colon cancer mortality. Notably, when the cancers were classified according to whether they were within or beyond the reach of the sigmoidoscope, a 60% reduction in risk was seen for cancers in the distal colon, and no reduction was seen for proximal colon cancers.

The frequency with which flexible sigmoidoscopy should be conducted is still debated [6]. A large case-control study revealed that the same reduction in mortality (70%) was seen whether a single sigmoidoscopy was conducted ten years prior to diagnosis or two years prior to diagnosis [90]. These results are consistent with the proposed timeframe of the adenoma-carcinoma sequence.

Utilization of screening

Despite their demonstrated effectiveness in reducing colon cancer mortality, FOBT and flexible sigmoidoscopy are not well utilized in the United States. In the 1992 National Health Information Survey, 26% of individuals over the age of 50 reported FOBT in the past three years, and 33% of individuals in this age range reported ever having had a screening sigmoidoscopy [91]. Vernon reviewed the demographic variables associated with colon cancer screening and the reasons for nonparticipation [91]. She found that women were more likely than men to complete FOBT, but men were more likely than women to be screened by sigmoidoscopy. Education and income were positively associated with both FOBT and sigmoidoscopy. There were no differences in FOBT screening by race, but blacks were less likely than whites to report sigmoidoscopy. In addition, perceived susceptibility was related to sigmoidoscopy; adherence to sigmoidoscopic screening was highest (69%) in relatives of colorectal cancer patients.

Summary of screening

FOBT and flexible sigmoidoscopy are currently recommended by the US Preventive Services Task Force for all asymptomatic men and women over the age of 50. FOBT is inexpensive and non-invasive, though it must be linked with more invasive follow-up procedures, such as colonoscopy, for those who screen positive. There is a high rate of false-positives, and the test must be done annually to be effective. Individuals who are screened regularly by FOBT may reduce their risk of colon cancer mortality by as much as 33%.

Flexible sigmoidoscopy is an invasive procedure and is more expensive than FOBT, costing $100–200 per procedure [6] compared to less than $10 per FOBT [81]. However, screening by flexible sigmoidoscopy is more effective than FOBT in reducing colon cancer mortality. Individuals screened by flexible sigmoidoscopy reduce their risk of colon cancer death by 50%. In addition, any polyps found during flexible sigmoidoscopy can be removed during the procedure; thus, flexible sigmoidoscopy is also related to a 42% reduction in colon cancer incidence. False-positive results are negligible, since biopsies are done during the procedure.

If screening by either of these methods were implemented on a population-wide level, colon cancer incidence and mortality could be substantially reduced. Large-scale screening efforts for breast and cervical cancer have been successful [2] and suggest that a population-based strategy aimed at colon cancer screening could be effective. In the next section, we discuss potential strategies to promote both screening and primary prevention of colon cancer.

5. Strategies for change

Despite the burden it poses to the United States, colon cancer is a disease that has been largely ignored by the public. Given the rapidly expanding understanding of the etiology of this disease, the public health community is in an excellent position to develop and implement strategies aimed at preventing colon cancer. Because it may take decades for such population-wide strategies to translate into a lower incidence of disease, initiatives aimed at colon cancer risk reduction should be implemented immediately. These strategies should focus on cultivating an environment that promotes policy initiatives, social norms, and, by extension, individual behaviors supportive of health. Such strategies, which we will discuss within the context of the United States, can be undertaken by health care providers, regulatory agencies, and communities (see Table 3).

Health care providers

Health care providers must make colon cancer prevention a priority and a norm within the health care setting. This can be accomplished by initiating discussions about colon cancer screening with all patients over the age of 50 and by counseling all patients about diet, weight control, and physical activity (see Table 4). While

screening is a disease-specific intervention, counseling on diet and activity is an intervention that targets multiple diseases, including cardiovascular disease, diabetes, osteoporosis, and many forms of cancer.

Given the wide range of screening options available for colon cancer, the provider and patient can select the screening test that is most appropriate and feasible. Studies of patient compliance rates for colon cancer screening suggest that patients are more likely to be screened if they are knowledgeable about colon cancer and believe in the importance of colon cancer screening [91]. In addition, patients are often embarrassed or uncomfortable with colon cancer screening [91]. Health care providers can obviously play an important role in improving compliance rates by providing adequate information about colon cancer, emphasizing the importance of early detection, and alleviating patients' fears and concerns about being screened.

Health care providers should also counsel all patients on diet and physical activity. Counseling needs to include a message about healthy behavior, as well as a discussion of barriers to behavioral change. This strategy has proven effective in motivating many healthy behavior changes, including physical activity [21]. A systematic review of published studies on this topic suggests that rates of smoking cessation can double, or even triple, by routine and repeated advice from health care providers [92, 93]. In addition, clinical trials conducted in the health care setting indicate that adults who receive individual counseling, as well as periodic monitoring and reinforcement, are more likely to make sustained improvements in their diets than adults who do not receive counseling and support [94].

Health care providers are most likely already counseling their patients on particular aspects of diet. This counseling should be expanded to include factors related to colon cancer. For example, one of the simplest recommendations providers can give their patients is to take a daily multivitamin. The Centers for Disease Control currently recommends that all women of childbearing age take a daily vitamin containing 0.4 mg of folic acid, since folic acid is protective against neural tube defects [46]. Assuming that providers are already making this recommendation to all women ages 15–45, it would be relatively simple to extend the recommendation to women over the age of 45 and to all men. The benefits of multivitamin use include likely reduction in risk of coronary heart disease and vitamin D insufficiency, which is common in northern parts of the United States during the winter months.

Table 3. Population-wide strategies to shift the distribution of modifiable risk factors for colorectal cancer

Risk factor	Strategy for change
Inactivity and obesity	Encourage communities to promote physical activity by restricting downtown urban areas to foot and bicycle traffic only and to build bicycling and walking paths in all communities.
	Offer tax incentives to employers who encourage employee physical activity, such as those who provide on-site facilities, allow flex-time for employees who commute by bike or foot, or offer wellness programs on physical activity and weight control.
Screening by flexible sigmoidoscopy or fecal occult blood test	Implement a wide spread education campaign for both providers and laypersons on the importance of early detection of colorectal cancer.
	Mandate insurance coverage of annual fecal occult blood tests and flexible sigmoidoscopy every 3–5 years.
Dietary factors (red meat, vegetable, and alcohol intake)	Provide adequate funding to strengthen the nutrition education component of all state health departments.
	Enforce the existing federal mandate that requires all schools participating in the National School Lunch Program to comply with Dietary Guidelines for Americans.
	Expand the number of farmers' markets through collaboration between state Departments of Agriculture, Departments of Public Health, and WIC. Expand the Farmers' Market Coupon Program by allowing vouchers to be used for vegetable plants, distributing coupons to repeat customers, and creating a more efficient coupon system as an incentive for farmers.
	Provide land and support for community gardens.
	All legal channels should be brought to bear to discourage youth drinking and heavy adult drinking.
	Promote school-based alcohol awareness programs.

Table 4. Behavioral messages for the prevention of colon cancer

Increase physical activity
Reduce red meat consumption
Take a daily multivitamin containing 0.4 mg of folic acid
Maintain a healthy weight
Increase vegetable consumption
Limit alcohol intake
Avoid smoking
Get screened regularly

Regulatory agencies

As the health care system makes colon cancer prevention a priority, government and industry may serve as regulatory agencies to ensure that all individuals have access to preventive services. This means addressing the many perceived barriers to screening, dietary change, and increased physical activity. In terms of screening, two of the most effective ways to ensure access are to remove the financial and time-related barriers. As of January 1997, Medicare offers coverage of colon cancer screening for all men and women over age 65. Other insurers may be encouraged to follow this example and extend coverage to those between ages 50 and 65. In addition to cost, lack of time is often a barrier to seeking preventive care [91]. An exemplary program that should serve as a model for the nation was instituted in Boston in 1998 by Mayor Thomas Menino. Mayor Menino enacted a policy that allows all city employees four hours off of work each year for cancer screening.

Federal, state, and local government can also play an important role in creating an environment that promotes physical activity and healthy eating. In January 1998, the Food and Drug Administration began requiring the fortification of all enriched grain products with folic acid [46]. Although this federal action was taken specifically to reduce risk of neural tube defects, it may also help to reduce risk of colon cancer by increasing folic acid intake in the general population.

On a state government level, healthy eating and daily physical activity should be promoted in all public schools. Because unhealthy behaviors related to colon cancer are often initiated at a young age, strategies aimed at children and adolescents are particularly important. Lesson plans teaching nutrition and physical activity concepts can be successfully incorporated into core academic subjects, allowing the teaching of preventive messages without taking away the teaching of subjects critical to academic success. Mandates requiring physical education for all students should be also enforced and expanded to include daily activity. State government should also enforce the existing federal mandate that requires all schools participating in the National School Lunch Program to comply with the Dietary Guidelines for Americans.

Local governments may also become involved in the promotion of preventive behaviors. For example, the city of Cambridge, Massachusetts, recently enacted a policy to make streets safer for pedestrians and cyclists. Whenever streets or sidewalks are being torn up for repaving, reconstruction, or sewage work, traffic-calming measures are incorporated into the reconstructed road, and bicycle lanes are created where possible. These mechanisms slow or re-route motor vehicle traffic, thereby increasing the likelihood of pedestrian and bicycle use within the city.

The role of industry in promoting primary prevention is two-fold. First, businesses can join in public–private partnerships with community and state organizations. Given the limited resources often available for prevention, this would allow for sharing of not only expertise, but also financial and material resources. Second, businesses can promote preventive behaviors among their employees. This could be accomplished by providing on-site kitchens, athletic facilities, and showers, allowing flex-time for employees who commute by bike or foot, and offering wellness programs on physical activity, dietary change, and weight control.

Community/Individual

Strategies implemented by both health care providers and regulatory agencies hinge on the role of the community. Local communities may support and enforce regulatory legislation, provide the manpower for prevention initiatives, or promote healthy activity and policies. An environment oriented toward prevention cannot be created without local, hands-on support at the community level.

In addition, one of the most important roles of the community is to spread awareness about colon cancer. Currently, most individuals are not aware that colon cancer is a leading cause of death and disease in the United States, and many do not adhere to colon cancer screening guidelines. The success of community-based interventions in changing cardiovascular risk factors, promoting mammography, and changing social norms around smoking suggests that communities could be equally effective in promoting colon cancer prevention.

Conclusion

Rigorous studies conducted on colon cancer biology and epidemiology in the past twenty years have led to a

rapidly expanding knowledge of this disease. We now have an excellent understanding of the natural history of colon cancer, as well as the factors that influence its development. We also have several effective screening tools to aid in the early detection of both adenomatous polyps and carcinomas. Based on this knowledge, over 50% of all colon cancers could be prevented through lifestyle changes and implementation of widespread screening. This translates into the prevention of 45,000 cases of colon cancer and nearly 24,000 deaths per year in the United States. To accomplish such a dramatic reduction in morbidity and mortality, we need to speed the implementation of screening, and facilitate change in lifestyle, as quickly as possible. We have acted far more quickly to prevent other diseases about which we have known less. It is time to utilize our vast knowledge of colon cancer to reduce the burden of disease in the United States.

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