REVIEW ARTICLE

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Primary and Secondary Prevention in Colorectal Cancer

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Colorectal cancer is an important public health problem: there are nearly one million cases of colorectal cancer diagnosed worldwide each year and half a million deaths. The geographic distribution of colorectal cancer follows the division between westernized versus developing countries. The highest rates are in North America, Australia and Europe. Rates in Africa and Asia are low, but are increasing in countries adopting western-style dietary habits. Given that the majority of cancers occur in older people, and with the ageing of the population in mind, this observation adds impetus to investigating prevention strategies to avoid some of this increase. High vegetable and fruit consumption has been associated with decreased risk of colorectal cancer in numerous observational studies, while high fibre intake seems to have a similar effect. Promising data have been obtained for aspirin and other non-steroidal anti-inflammatory drugs, and dietary calcium. A physically active lifestyle and maintenance of normal body weight are behavioural tools for prevention of colorectal cancer. Faecal occult blood testing has been shown to be effective in the prevention of about 20% of deaths from colorectal cancer, but few population-based screening programs have been initiated. Sigmoidoscopy and colonoscopy are potentially effective screening modalities; however, no randomized trial data have yet been reported. Overall, primary and secondary prevention, chemoprevention and screening research and implementation of these prevention strategies are priorities for reduction of colorectal cancer incidence and mortality.

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Globally, colorectal cancers rank third in the frequency of incidence (945 000 new cases, 9.4% of the world total) and mortality (492 000 deaths, 7.9% of the total), with similar numbers in men and women (1). The incidence of large-bowel cancer is high in North America, Western and Northern Europe, Australia/New Zealand and low in Africa and Asia. The geographic distribution of colon cancer and rectal cancer is similar.

The large geographic differences probably represent the effects of different environmental exposures, presumably mainly dietary. It has long been evident from migrant studies that the risk of colon cancer is fairly labile to environmental change, and that changes can occur within 10–15 years, even in adults (2, 3).

Incidence rates have been increasing in some countries where previously they were low, whereas in high-risk countries, there has been stabilization or decrease in incidence, particularly in the younger age groups. For mortality, the pattern is similar, with an increase for countries with the low initial rate (Eastern Europe, Japan, Singapore), small increases in countries with moderate rates, and a decrease for high-rate populations (Western Europe, North America) (4, 5).

Clearly, colorectal cancer is an important public health problem, not only for countries with a western lifestyle but increasingly in other parts of the world. The ageing population worldwide coupled with the propensity for most colorectal cancers to occur over the age of 50 will have an obvious impact on the global burden of colorectal cancer unless effective control action is taken.

VARIOUS MODES OF PREVENTION

Primary prevention refers to an intervention that is usually applied to a general, 'healthy' population at average risk for disease: to counteract the effect of a cause of the disease, or to administer some type of prophylactic to those susceptible to the disease. Primary prevention may also refer to preventive treatment given to individuals. 'Chemoprevention' is a term that has been widely used to describe intentional chemical interference with the process of carcinogenesis by inducing a variety of biological mechanisms. Chemoprevention can be achieved by preventing the onset of carcinogenesis by protecting against initiation or by arresting or reversing later stages of carcinogenesis at various steps in the processes of promotion and progres-

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sion. The use of agents to prevent cancer in apparently healthy individuals falls within the framework of '*primary prevention*'. However, because even in high-risk populations the average lifetime risk of colorectal cancer only approximates to 1 in 20, the agents given must be exceptionally safe, yet effective in achieving the major goal of primary prevention—reducing the incidence of the disease.

In '*secondary prevention*', a screening test is applied in an asymptomatic population to detect abnormalities among individuals with subclinical disease—thus identifying those who are at greater-than-average risk for clinically evident disease—for the purpose of subsequently intervening to reduce their risk. Chemoprevention used to arrest or reverse carcinogenesis in individuals who have been identified as having a pre-malignant lesion falls within the framework of secondary prevention (the prevention of disease at a preclinical stage). '*Tertiary prevention*', defined as the prevention of complications (recurrence, invasion, metastases) among people already diagnosed with symptomatic disease, is best regarded in the context of clinical management of cancer patients.

DIFFERENT AETIOLOGIES AND MECHANISMS

In considering various mechanisms on which preventive factors might influence the incidence of cancer, it is necessary to reflect on varying aetiologies of different types of cancer. The most immediate cause of cancer is damage to DNA at some stage during the cell cycle. At the risk of oversimplification, this can arise from one of three broad mechanisms:

i) The first mechanism is *genetic*, with obvious examples being certain childhood cancers, certain forms of breast cancer, as well as disorders causing abnormalities that have a high probability of malignant transformation, such as familial polyposis coli.
ii) A second group of cancers is linked with *endogenous hormonal patterns*. The association between reproductive history and breast cancer is perhaps the best-known example, although there are some indications that endogenous hormones may also influence the risk of colon cancer.
iii) A third mechanism involves the action of *exogenous carcinogens*. By far the most important for cancer generally are those compounds produced from tobacco. Others include a wide range of other chemical, physical and biological agents. A subgroup comprises the endogenous production of carcinogens from the interaction of substances that are themselves not carcinogenic.

These three factors/mechanisms may, of course, act together in certain cases. Thus, the risk of colorectal cancer appears to be influenced by diet and, by implication, exogenous or endogenously produced carcinogens. The exploration of the metabolic links between these macroscopic factors and cancer occurrence is just beginning. There are strong biological reasons to think that diet and lifestyle can have an effect on the development of several cancers, including colon cancer, through modification of the endogenous hormonal milieu. Complex hormonal mechanisms involving oestrogens, androgens and their transport globulin (SHBG), as well as insulin, insulin-like growth factors (IGFs and GH) and their transport proteins may play an important, yet not fully understood role in the aetiology of cancer. Another important area of research includes a variety of bioactive endogenous compounds such as prostaglandins, thromboxanes, leucotriene, etc., which may be partially regulated by nutritional factors.

Almost unexplored is the wide field of inter-individual variations in sensitivity to nutritional factors, as modulated by genetic characteristics and non-dietary lifestyle exposures such as those related to the complex interaction of inherited genetic characteristics and lifestyle factors other than diet (6, 7).

PUTATIVE CANCER PREVENTIVE AGENTS IN DIET

The WCRF/AICR review of the literature to about 1995 (6) concluded that the evidence for vegetables decreasing cancer risk was convincing for colorectal cancers. Interestingly, the WCRF/AICR review does not mention fruits with regard to colorectal cancer in their summary. In a specific section later they say, 'the data on fruits are more limited and inconsistent, no conclusion is possible' (6). The IARC has recently completed an evaluation of the published scientific literature (8). The evidence indicates that a higher intake of vegetables probably lowers the risk of cancers of the large bowel. Likewise, a higher intake of fruits possibly reduces the risk of colorectal cancer. Overall, it is likely that the levels of fruit and vegetable consumption will reduce the incidence of various cancers, while also lowering the risk of various other non-communicable diseases (8, 9).

Dietary fibre is thought to protect against the development of colorectal cancer, and consensus reports have recommended an increase in fibre for populations consuming low amounts in order to reduce relatively high rates, though this has been challenged by more recent studies. Within the ten European countries studied in the Investigation into Cancer and Nutrition (EPIC), mean fibre consumption varied substantially across quintiles from 13 g/day to 35 g/day. Results from the EPIC showed that dietary fibre intake was inversely related to large bowel cancer incidence. Using the 38 000 individual 24-h diet recalls, questionnaire measurements of fibre intake were calibrated across countries, and relative risks were corrected for attenuation due to random measurement errors. Based on a linear trend analyses, the RR for consumption of 35 g/day compared with 15 g/day was 0.58 ($p < 0.001$). The greatest protective

effect was found to be for the left side of the colon, and least for the rectum. Fibre from cereals was more strongly protective than fibre from vegetables, fruit and legumes, although the difference in effect was not statistically significant (10).

Among 15 538 middle-aged male smokers in the ATBC study in Finland, an increased risk was reported for colorectal adenomas in the group receiving alpha-tocopherol supplementation compared with the no-alpha-tocopherol group (11). Because the study population was not screened for colorectal polyps before the study, and no systematic screening was performed during the trial, there is a possibility that the apparent increase in adenomas was, at least partly, due to a bias caused by alpha-tocopherol inducing increased bleeding and intestinal pain leading to more colonoscopies in those with pre-existing polyps, and thus, increased apparent incidence of polyps. This interpretation is supported by the fact that vitamin E supplementation had no effect, or perhaps even a slight preventive effect, on colorectal cancer risk in the trial (12).

In a double-blind trial the effect of vitamin C (3 g/day for 2 years) on patients with familial adenomatous polyposis (FAP) was investigated (13). A significant reduction in polyp area was noticed in this trial, as well as a trend towards reduction in polyp number during some periods of the study. This suggests that vitamin C may have an effect on polyp promotion, as well as a possible slight effect on initiation.

CHEMOPREVENTION OF COLORECTAL CANCERS

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) show great promise in the chemoprevention of colorectal cancer (14). Use of aspirin needs to be balanced against the risks of toxicity and other beneficial effects such as prevention of cardiovascular morbidity and mortality. Some of the NSAID-induced gastric ulceration and bleeding will most likely be prevented by adopting the use of COX-2 specific NSAIDs, which will selectively inhibit COX-2 while sparing COX-1.

A problem in the evaluation of causality of the association between aspirin use and colorectal cancer reduction has been a relative lack of randomized trial data. In this regard, Sturmer et al. (15) published the post-trial follow-up data from the Physicians' Health Study. After the aspirin arm of the randomized study was stopped in 1988, participants chose to receive aspirin or placebo for the rest of the study. Seventy-one percent of the participants chose to continue taking aspirin along with beta-carotene or placebo. No difference was found in colorectal cancer risk between participants not taking aspirin, those who stopped taking aspirin in 1988, those who started taking aspirin after 1988 and those who had taken aspirin throughout the entire study period. The authors acknowledge that the 'the low dose of aspirin used and the short treatment period may account for the null findings'. Thus, with aspirin, we are in the situation where the observational epidemiological evidence strongly suggests a protective effect of regular aspirin intake, whereas the 'gold standard', the randomized clinical trial, suggests no protection against colorectal cancer formation, under the same conditions where the clinically important protective effects of aspirin in prevention of cardiovascular mortality were demonstrated.

Two trials have been published recently in which aspirin reduced the rate of recurrence of adenomas (16, 17). In the study by Sandler et al. (16) 635 patients who were cured of colorectal cancer were randomly assigned to receive 325 mg aspirin or placebo daily. The trial was terminated after a median duration of 31 months because one or more adenomas were discovered in 17% of patients in the aspirin group and 27% of those in the placebo group. The hazard ratio for detection of a new polyp in the aspirin group as compared with the placebo group was 0.64, indicating that aspirin delayed the development of adenomas.

In the study by Baron et al. (17), 112 patients who had recently had adenomas removed were assigned to placebo, to 81 mg aspirin daily, or 325 mg aspirin daily. After a mean duration of 33 months, advanced neoplasms were found in 12.9% of patients in the placebo group, 7.7% of those in the 81 mg group, and 10.7% of those in the 325 mg group. The rate of recurrence of adenomas was significantly lower in the group taking low-dose aspirin than in the placebo group, but for reasons that are unclear, the larger dose of aspirin did not significantly reduce the rate of recurrence.

Dose-duration considerations for aspirin may help to reconcile some of the conflicting data for colorectal cancer chemoprevention. Some studies suggest that 10 years of aspirin consumption may be required for protection and this would account for the negative findings reported by Sturmer et al. (15). However, as suggested by the recent trial of Baron et al. (17), the dose of aspirin required for chemoprevention may well be in the low range that reduces cardiovascular disease risk (75–100 mg) and this has far-reaching public health implications.

Most recently, the Food and Drug Administration (FDA) (USA) has approved the NSAID celecoxib, which is a selective COX-2 inhibitor, to reduce the polyp burden of FAP patients. The FDA approval was based on a trial of 77 FAP patients, which showed a significant 28% reduction in mean polyp number (vs. 4.5% in the placebo group) using 400 mg celecoxib twice daily for 6 months (18). Although this trial has potentially important implications for patients with FAP, it is unclear at present how relevant it will be to colorectal cancer prevention generally. A trial in patients diagnosed with adenomatous polyps who do not suffer from FAP would potentially be very informative.

Despite the consistent efficacy of some NSAIDs, especially sulindac, against colorectal adenomas in FAP, there is still some need for caution before prescribing this approach

as the remedy for all malignant disease in heritable colorectal cancer syndromes. At least three reports have documented incident cancer cases occurring among FAP patients while on sulindac (19–21). Such cases highlight the fact that an accurate estimate of long-term colorectal cancer risk reduction from sulindac in individuals with FAP cannot currently be made. Any benefit of these agents is likely to be transient, since an increase in the number and size of polyps has been noted in patients three months after sulindac is discontinued (22, 23). Furthermore, it might be speculated that single chemopreventive agents may not prevent all neoplastic lesions because oncogenesis probably involves dysregulation of multiple cell growth and death pathways. For effective chemoprevention in the setting of strong genetic or environmental influences, combinations of agents working through complementary mechanisms may prove optimal.

In hereditary nonpolyposis colorectal cancer (HNPCC), chemopreventive drug testing and development have been limited, partly owing to the lack of a relevant animal model. In clinical studies, only calcium has been tested among persons with increased familial non-polyposis colorectal cancer risk, and the results with this agent were inconclusive. There are several chemoprevention trials underway, on celecoxib (COX-2 specific inhibitor in the USA) and another to test aspirin and resistant starch on adenoma prevention by a European study group.

PHYSICAL ACTIVITY AND WEIGHT CONTROL

Evidence from observational studies indicates that physical activity may reduce the risk of several types of cancer, including cancers of the colon and breast (24). Physical activity acts in a variety of ways to impact cancer risk. Regular physical activity helps maintain a healthful body weight by balancing caloric intake with energy expenditure. Other mechanisms by which physical activity may help to prevent cancer involve both direct and indirect effects. For colon cancer, physical activity accelerates the movement of food through the intestine, thereby reducing the length of time that the bowel lining is exposed to food ingredients. It may also improve energy metabolism and reduce circulating concentrations of insulin and related growth factors.

Overweight and obesity are associated with increased risk for cancers at several sites, including colon and adenocarcinoma of the oesophagus (24). Individuals should strive to maintain a body mass index between 18.5 and 25 kg/m^2. As yet, there is no study which convincingly demonstrates that losing weight reduces the risk of cancer, although there are biologically plausible mechanisms to suggest that weight loss may be beneficial. Overweight or obese individuals who intentionally lose weight have reduced levels of circulating glucose, insulin and bioavailable oestrogens and androgens. One major class of mechanisms that may link cancer risk to nutrition is excess energy intake (25, 26) and related alterations in endogenous hormone and growth factor metabolism (27–29). Excess weight and physical inactivity lead to insulin resistance and chronic hyperinsulinaemia, which has been hypothesized to be a causal factor in the aetiology of cancers of the colon (29).

IMPACT OF SCREENING ON MORTALITY AND INCIDENCE OF COLORECTAL CANCER

The US Commission on Chronic Illness (30) defined screening as the 'presumptive' identification of unrecognized disease or defect by the use of tests, which can be applied rapidly. A screening test is not diagnostic. Individuals with positive findings should be referred for diagnostic tests and appropriate treatment.

Faecal occult blood test

The results of three randomized trials of faecal occult blood test (FOBT) have been published (31–34). The mortality reduction was 33% when the test was offered annually and 15–20% when it was offered every two years. The Minnesota trial used a rehydrated test, which increased sensitivity at the expense of greatly decreased specificity. A meta-analysis showed that with two-yearly screening, the number needed to be screened to prevent one death from CR cancer over 10 years is 1 173 (741—2 807) (35). In the first reports of the studies no impact on incidence was shown; more recently (36) a reduction in incidence rates of 17–20% was shown with 18 years of follow-up of the Minnesota trial participants. The reduction is thought to result from the detection of large adenomas by the diagnostic colonoscopies that followed a positive FOBT.

Rigid and flexible sigmoidoscopy

Several studies have explored the role of primary endoscopy in screening (35, 37–44). Rigid sigmoidoscopy has been replaced by flexible sigmoidoscopy in more recent studies.

Following rigid sigmoidoscopy, a consistent 60–80% decrease in the incidence of, or mortality from distal bowel cancer has been observed (Table 1), suggesting that the detection and removal of adenomatous polyps reduce the incidence of CR cancer. However, most of these analyses had methodologic flaws, in particular when invasive cancers found at the initial prevalence screen were not taken into consideration (37). Therefore, randomized trials are essential to confirm the presumed beneficial effect of endoscopic screening. Unfortunately, only one randomized, controlled trial has been reported, and this was too small to demonstrate a beneficial effect of polyp removal (44). Some observational studies, however, have shown an apparent beneficial effect. The most influential of these studies is a case-control study (38), undertaken using Kaiser Permanent Health Maintenance Organization (HMO) records, which compared the exposure to sigmoidoscopy

Table 1

Studies of the efficacy of sigmoidoscopy in the prevention of distal colorectal cancer

Authors	Year of publication	No. of cases	Reduction in incidence (or mortality*)	Type of study
Gilbertsen & Nelms (48)	1978	27 000	60–85%	Prospective cohort
Friedman et al. (49)	1986	10 713	60%	Randomized, symptomatic trial
Atkin et al. (50)	1992	1618	85%	Retrospective cohort
Selby et al. (38)	1992	1129	70%*	Case-control
Newcomb et al. (51)	1992	66	79%*	Case-control
Muller & Sonnerberg (43)	1995	32 702	40%	Case-control
Thiis-Evenson et al. (52)	1999	800	80%	Case-control

screening during the previous 10 years in cases (diagnosis of fatal colorectal cancer) and in age- and sex-matched controls (no cancer). It was found in this study that sigmoidoscopy screening reduces deaths from distal colorectal cancer by 60%. Sigmoidoscopy had no effect on reducing the deaths from cancer in the proximal colon beyond the reach of the instrument.

Three randomized trials of flexible sigmoidoscopy (FS) screening are in progress: the Prostate, Lung, Colorectal and Ovarian (PLCO) trial in the USA is examining the efficacy of FS screening repeated at 5-year intervals (39), while in trials in the UK (40) and in Italy (41) a single FS screen offered at age 55–64 years is being evaluated.

Colonoscopy

Evidence for the efficacy of colonoscopy screening in reducing CR cancer incidence is based on uncontrolled cohort and case-control studies. The National Polyp Study (42) followed 1 418 people (for 6 years) who had undergone a colonoscopy for removal of an adenoma and compared the number of cancers in the cohort with the number expected based on other similar series of patients who had not undergone the procedure. They concluded that colonoscopy screening reduces incidence by 75%. However, the analysis did not preclude the methodologic flaw discussed above for the sigmoidoscopy studies. Furthermore, most of the cancers that developed during follow-up were located beyond the reach of a sigmoidoscope, so it is not clear how much increased benefit was derived by examining the right colon. In two case-control studies, no additional benefit of colonoscopy was observed in comparison with flexible sigmoidoscopy (43, 44).

POSSIBLE TARGET GROUPS FOR SCREENING FOR COLORECTAL CANCER

Average risk individuals

A number of recommendations are based on age only. The Task Force recommended in 1996 that all persons over the age of 50 years should be offered either FS or FOBT, or both (45). In the UK, where colorectal cancer screening is not currently offered, a pilot study is underway to examine the feasibility of offering FOBT every 2 years to patients between the ages of 50 and 69 years. In this pilot study, people over 69 years of age are not invited to have the test, but can request it.

Individuals at moderately increased risk

Colorectal cancer is moderately increased in individuals who have a family history of colorectal cancer. The risk is about twice the average population risk if one first-degree relative has been affected; the risk at age 40 years is considered equivalent to that of a 50-year-old at population risk. As many as 15% of all colorectal cancers may occur in individuals from this moderate risk group. Thus, if it is decided to initiate a screening program in a population, special attention should be made to ensure that the public understands those circumstances where they are at increased risk.

High-risk individuals

Susceptibility to colon cancer can be predicted on the basis of a family onset of the disease, particularly when this involves early age of onset (46). Other relevant factors include age and gender, increasing risk being associated with increasing age and being of male sex. Groups that merit specific clinical surveillance include those at higher risk because of a family history including FAP and HNPCC, and individuals with family histories of colorectal cancer which do not meet the criteria of well-defined syndromes, but which appear to follow the inheritance patterns of those that do. About three quarters of colorectal cancers are thought to be due to sporadic somatic mutations in critical genes, and both high- and low-penetrance predisposing genes contribute to the remaining quarter of cases. Many of the highly penetrant dominant genes are known, but others remain to be identified.

Establishing genetic susceptibility for colorectal cancer will soon be possible, and could save lives by allowing targeting of screening and the promoting of preventive therapies and behaviours. However, there will always be a risk of making 'healthy' people 'sick' through the identifica-

tion of predisposing genes, and it could be that a gene carrier might be stigmatized by society, insurance companies and employers.

PREVENTION OF COLORECTAL CANCER: FROM DREAM TO REALITY

Great progress has been made in cancer prevention during the past two decades. Nevertheless, the field could benefit from the experiences of investigators studying the prevention of cardiovascular disease (47). During the past 50 years, prevention of cardiovascular disease has gone from dream to reality, with major clinical impact. The trend during the last 30 years has been impressive and sustained. This trend is believed to have resulted from improvements in treatment of myocardial infarction and, more substantively, from improvements in primary prevention (i.e. reduction in smoking and serum cholesterol) and secondary prevention (i.e. treatment of hypertension).

FOBT has proven effective in preventing mortality from colorectal cancer in several randomized trials. However, FOBT testing is not without problems: the greatest difficulties relate to its low compliance in general population studies, and its relative inability to detect precancerous lesions and its production of a large number of false-positive results. Obviously, there is a need to develop a more effective and reliable test. Flexible sigmoidoscopy has also produced promising results; however, randomized trial data are awaited to demonstrate its efficacy in decreasing mortality from colorectal cancer. 'The big elephant in the room' when it comes to colorectal cancer is colonoscopy. Evidence for its benefit is only indirect, and the rates of compliance, accuracy and complications are not known in situations where it would be done on a widespread basis. Before advocating widespread screening by colonoscopy, we would need to know the benefit-to-harm ratio, which is why we need a randomized screening trial.

The tools are now available to make prevention of colorectal cancer a clinical reality. As preventive science improves, it must be remembered that effective and efficient preventive services do not help if they are not used. It may be difficult to motivate practitioners and people to implement these services. Furthermore, preventive services are often considered a luxury. The most effective colon cancer prevention programme will probably use rational primary prevention, targeting specific risk factors, promoting public health through healthy lifestyle, avoidance of weight gain, encouragement of physical activity and a healthy diet with enough vegetables and fibre, efficient screening tools for early detection and treatment of cancers, and possibly chemoprevention to prevent recurrences among those identified with precancerous lesions, or prevention of second primary tumours among those who have already had one colorectal cancer.

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