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Chemo- and Dietary Prevention of Colorectal Cancer

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Because of the substantial morbidity and mortality associated with colorectal cancer, and the limitations and costs of treating this disease, prevention remains a desirable (if elusive) goal. In this paper, we discuss both chemo- and dietary prevention strategies for colorectal cancer, recognising the overlap and cross-fertilisation between these two approaches. Chemopreventive compounds are drugs and are developed for clinical use like other pharmaceuticals. A formal sequential multi-phase programme for development of chemopreventive agents has been instituted by the National Cancer Institute, U.S.A. This involves both preclinical efficacy and clinical studies. Such studies increasingly employ preneoplastic intermediate markers (such as proliferation measures) as well as neoplastic adenomas as endpoints. Promising chemopreventive agents include calcium, aspirin and other non-steroidal anti-inflammatory drugs, vitamins (such as vitamin E and folate), 2-dimethylfluornithine (DFMO), oltipraz and ursodeoxycholic acid. Several lines of evidence implicate diet in colorectal carcinogenesis. Key hypotheses in diet and colorectal cancer (which are amenable to prevention, research and action), in addition to those pertaining to the micronutrient chemopreventives, include dietary fat and fibre, food mutagens, red meat, and overall low-fat, high-fibre, high fruit and vegetable dietary patterns and cuisines. Several adenomatous polyp recurrence studies with fibre supplement, macronutrient or dietary pattern interventions have been undertaken internationally. We review early findings from this new generation of studies, and anticipate the future results from these investigations and the ambitious Women's Health initiative in the U.S.A. Results from these studies may convert the promise of colorectal cancer prevention into reality.

Key words: dietary prevention, chemoprevention
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INTRODUCTION

PREVENTING COLORECTAL cancer and reducing the incidence of the disease remains compelling goal. The search for practical preventive strategies can be justified on several counts.

Morbidity and mortality associated with the disease are substantial. In the U.S.A. alone, nearly 60 000 deaths each year are attributed to colorectal cancer, making it the second leading cause of cancer mortality among men and women combined [1].

Treatment is less than 100% effective. Nearly 150 000 men and women are diagnosed yearly in the U.S.A. with this disease. In spite of advances in treatment over the last decade, 5-year survival remains only approximately 50% [1].

Early detection may reduce but will not eliminate deaths from this malignancy. Recent studies suggest that early detection with faecal occult blood testing and other modalities can reduce mortality from colorectal cancer [2], although there are likely to be limits on the extent to which potentially advanced disease can be detected in more localised states. Furthermore, there is some mortality associated even with relatively localised cases.

Treatment, even when successful, incurs substantial economic (and psychological) costs. The cost of colorectal cancer treatment in 1990 in the U.S.A. was recently estimated at approximately $6.5 billion [3]. The psychological burden imposed by diagnosis and treatment of this potentially lethal disease is certainly considerable, if difficult to calculate.

IS IT POSSIBLE (AND PRACTICAL) TO PREVENT COLORECTAL CANCER?

Preventing malignant disease means interfering in the causal chain implicit in the carcinogenic process. The most familiar (and, to date, successful) approach to interfering with this process is simply eliminating or reducing exposure to carcinogenic agents. Cigarette smoking, for example, has long been established as the major (and modifiable) cause of lung cancer in Western countries. The evidence clearly indicates that population-wide reduction of cigarette smoking (and possibly the substitution of lower tar cigarettes) reduces lung cancer rates [4].

As our understanding of the mechanisms of carcinogenesis has grown, possibilities have emerged for moving beyond simple avoidance of exposure and interfering at multiple points along the carcinogenic spectrum. Many specific microprocesses have been proposed as biological targets for both chemo- and dietary preventive activity [5]. A variety of chemical compounds, whether considered singly as pharmaceutical agents or consumed in foods (in combination with many other nutrients and non-nutritive constituents), may modify the ability of carcinogens to interact with tissue. This may comprise inhibiting carcinogen

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activation, promoting deactivation or interfering with cellular uptake. Other proposed mechanisms of preventive action include modulating proliferation and progression of precancerous cells and lesions, inhibiting aberrant signal transduction, inducing terminal differentiation and apoptosis, enhancing immune surveillance and restoring tumour suppressor function.

THE CHEMOPREVENTION STRATEGY

One can distinguish (although not rigidly) between chemoprevention and dietary prevention strategies. Cancer chemoprevention has been defined as the use of specific chemical compounds to prevent, inhibit or reverse carcinogenesis [6], whereas dietary prevention involves the modification of foods or dietary patterns (often accompanied by substantial lifestyle changes) to influence cancer development. There is considerable overlap between these two approaches: many nutrients and other non-nutritive components of foods, when considered in isolation, are potential chemopreventive agents.

Chemopreventive compounds are drugs, and they are developed for clinical use like other pharmaceuticals. These agents are intended for administration at specific doses according to defined regimens. Many promising chemopreventive agents (non-steroidal anti-inflammatory drugs (NSAIDs), for example) are drugs already approved for other purposes.

Like other pharmaceuticals, investigators may design chemopreventives to maximise their specificity in reaching target tissues by taking advantage of the agents' pharmacokinetic parameters, and using appropriate routes and modes of administration. This specificity may permit lower doses of agent to be given, and thereby reduce potential side-effects resulting from higher concentrations in non-target tissues. An example relevant to chemoprevention of colorectal cancer would be an NSAID that avoids the toxicity to gut mucosa associated with oral NSAID administration. The prodrug, ampiroxicam, for example, is not converted to the NSAID piroxicam until it reaches the small intestine [7].

It is important to note important differences between chemoprevention and chemotherapy. Whereas chemotherapeutics are given for short periods of time or in discrete cycles to patients with diagnosed malignancies, chemopreventive agents must have minimal toxicity because of their long-term administration to relatively healthy individuals. Moreover, chemopreventives are given to prevent cancer rather than cure already invasive disease. It follows that the developmental paths for chemotherapeutics [8] and chemopreventives also differ substantially. Nevertheless, there is overlap conceptually and practically between chemoprevention and chemotherapy. Chemoprevention agents may yield benefit as adjuvant treatment to prevent recurrences or new primary tumours in patients already treated for cancer. Furthermore, some of the mechanisms underlying chemopreventive and chemotherapeutic action are similar. Like some chemopreventive agents, cytostatic chemotherapeutic agents slow the growth and progression of dysplastic cells (for example, by inducing terminal differentiation).

INVESTIGATION OF POTENTIAL CHEMOPREVENTIVE AGENTS

The National Cancer Institute (NCI), U.S.A. and the U.S. Food and Drug Administration have collaborated to provide conceptual and practical guidance for developing cancer chemopreventive agents. The NCI programme covers all aspects of drug development, including discovery of candidate agents, preclinical efficacy, pharmacological toxicity and pharmacokinetics, and clinical trials. The approach includes characterising efficacy of candidate drugs using *in vitro* transformation modulation and animal tumour models.

In most animal chemoprevention models, a carcinogen such as dimethylhydrazine or methylazoxymethanol is administered at a high enough dose to induce a significant incidence of tumours in the target tissue. The appropriate carcinogen dose and treatment schedule are selected to ensure that the efficacy of the potential chemopreventive agent is not masked by carcinogen toxicity. The test agent is usually administered in the diet unless there are problems with its stability or absorption (for example, beta-carotene is poorly absorbed in rats on oral administration). Tumour incidence and multiplicity are the common endpoints in these animal studies, although there is increasing interest in examining intermediate endpoints, such as aberrant crypt foci [9].

Short (1 month to 3 years) trials (phase II) using intermediate endpoints, such as proliferation markers, are carried out to provide evidence of human efficacy. These intermediate biomarker studies typically involve from several dozen to up to a few hundred participants. If, in studies with proliferation marker endpoints, the treatment reduces labelling indices (or, alternatively, redistributes proliferation from the upper to basal regions of the crypt), then the investigator has evidence to justify testing the agent in a more definitive (phase III) trials with neoplasia endpoints. These studies, which may involve adenoma recurrence, adenoma growth or even incident cancer as an endpoint (see discussion below of Women's Health Initiative), are longer and larger than the studies with non-neoplastic endpoints. Results from these trials, however, are far more compelling than those from proliferation and other non-neoplasia endpoint studies.

Adenomatous polyp trials are attractive compromises between proliferation and other biomarker studies, with their limited inferential strength, and full-scale cancer endpoint trials with their daunting logistical and sample size requirements. There are several reasons for using adenoma endpoints in colorectal cancer prevention research.

The relatively high prevalence of colorectal adenomas in industrialised countries, over 50% among older age groups in autopsy studies, creates a large pool of potential participants for trials [10].

The recurrence rate of colorectal adenomas has been demonstrated in several studies to be in the range of 10% or more annually [10]. This rate, some two orders of magnitude greater than the colorectal cancer incidence rate, permits an adenoma recurrence trial to be conducted with far fewer participants than would be required in a colorectal cancer endpoint study.

Standard surveillance following adenoma removal has, in the past, frequently meant one or more repeat colonoscopies. The integration of standard clinical practice into trial designs permits trial investigators to have study participants examined for recurrent adenomas as part of standard clinical practice. Because the required number of participants in a polyp trial depends, in part, on the number and frequency of follow-up colonoscopic procedures, recent shifts in recommended frequency of follow-up colonoscopy [11] will require changes in polyp trial design, such as the elimination of the 1-year follow-up.

The theoretical biological rationale for adenoma recurrence as a trial endpoint is the well-established adenoma–carcinoma sequence. Adenomas are considered necessary precursors of most colorectal cancers, even though only a small proportion of adenomas become malignant. A substantial body of clinical,

pathological and epidemiological data support the concept of an adenoma–carcinoma sequence; recent findings from cell [12] and molecular [13] biology lend further support.

Some adenomas may be more likely to undergo malignant transformation than others. At the present time, we can do little more than crudely assign a gradation of malignant potential, based on such features as size or histology, to each adenoma. It is possible, although by no means proved, that certain ("innocent") polyps have no malignant potential. If this is the case, then drawing inferences from polyp trial findings to colorectal cancer becomes more problematic.

If adenoma recurrence is lower in the intervention than the control group ("positive result"), the most reasonable interpretation is that the intervention also reduces the incidence of colorectal cancer. An alternative interpretation, however, is that the intervention reduces the development of innocent adenomas, but has no effect on the occurrence of those ("bad") adenomas with malignant potential meaning, therefore, that the intervention has no effect on colorectal cancer. This alternative interpretation is arguably quite unlikely, but currently, we have no technical tools enabling us to reliably distinguish "innocent" and "bad" adenomas, and thereby rule out this alternative explanation.

If adenoma recurrence is the same in the intervention and control groups (a null result), the primary interpretation is that the intervention does not reduce colorectal cancer incidence. Here, though, several alternative interpretations are possible. (a) The intervention may reduce development of those adenomas with malignant potential, but not affect those without such potential. The intervention truly lowers colorectal cancer incidence, even though a statistically significant reduction in total adenoma recurrence is not observed. (b) The intervention does not affect the development of small adenomas, but does inhibit the growth of small into large ones, wich are more likely to develop into carcinomas. Therefore, the intervention would reduce colorectal cancer incidence. (c) The intervention was not administered for a long enough time. (d) The intervention was not administered early enough in life. (e) Follow-up time was inadequate; a positive finding would have emerged with a longer period of observation.

Although evidence exists to argue against each of these alternative explanations—for example epidemiological studies show that risk factors associated with colorectal cancer are also associated with small adenomas [14]—none of these alternatives can be ruled out categorically. Because findings from polyp trials cannot demonstrate conclusively that the intervention affects colorectal cancer in the same way that it does adenoma recurrence, results from adenoma recurrence trials should be evaluated in conjunction with results from other types of colorectal cancer investigations, particularly well-designed epidemiological studies (that have explicit cancer endpoints).

We note an inferential asymmetry for polyp trials, with the alternative interpretations of a positive finding being fewer and less likely than those from a null finding. In other words, positive results are more persuasive, with respect to colorectal cancer, than null results. This inferential asymmetry is a common feature of many clinical trials.

PROMISING AGENTS FOR COLORECTAL CANCER CHEMOPREVENTION

Calcium

The chemopreventive activity of calcium was first suggested by epidemiological studies showing an inverse relation between dietary calcium or milk intake and colorectal cancer [15]. Subsequent animal studies have demonstrated inhibition of colon carcinogenesis by calcium salts.

A physiological explanation for calcium's chemopreventive activity derives from animal and *in vitro* studies showing that excess free bile acids and unabsorbed fatty acids promote carcinogenesis by irritation of and damage to the colorectal epithelium. This damage induces compensatory proliferation and expansion of the proliferative compartment. Calcium administration decreases the proliferative stimulus by binding with the lipid products to form insoluble calcium soaps. Calcium is also involved in membrane integrity, cellular differentiation, proliferation and death, as well as intra-and intercellular signalling. Calcium administration in humans has been shown to inhibit colorectal proliferative activity, but this has not been confirmed in all studies. There are clearly several plausible biological explanations for why calcium might inhibit colorectal carcinogenesis [15].

Several phase II and III trials are now underway, including at least two large adenoma recurrence trials. The potential chemopreventive combination of calcium carbonate with vitamin D_3 is under investigation; the bioactive metabolite of vitamin D_3 promotes transport of calcium from the intestinal lumen and maintains serum calcium homeostasis. The Women's Health Initiative (discussed below) has the capacity to investigate the effect of a combination of calcium and vitamin D_3 on colorectal cancer incidence. Calcium and vitamin D's effects on colorectal cancer are reviewed by Kleibeuker and associates in this issue (pp. 1081–1084).

NSAIDs

These compounds have generated great interest as possible agents for the chemoprevention of colorectal cancer. We briefly discuss four examples: aspirin, ibuprofen, piroxicam and sulindac. NSAIDs are reviewed in this issue by Giardiello and associates (pp. 1071–1076).

Aspirin. Like the other NSAIDs, aspirin's anti-inflammatory activity derives from inhibition of prostaglandin (PG) synthesis through inhibition of the cyclo-oxygenase activity of PGH_2 synthase [16]. Unlike the other NSAIDs, it is an irreversible inhibitor of the enzyme. PGs may enhance carcinogenesis by proliferation induction, mutagenesis, formation of reactive oxygen species or immune system suppression. The enzymes involved may also activate certain carcinogens by co-oxidation.

A number of epidemiological studies have shown a protective association for aspirin use in relation to colorectal cancer incidence or mortality [17]. However, a recent randomised trial of aspirin for prevention of cardiovascular disease, showed no inverse relation between aspirin and occurrence of colorectal cancer [18]. Aspirin has shown chemopreventive activity in animal carcinogen models.

A number of phase III trials are now underway. The Women's Health Study (Dr J.E. Buring, Harvard University, U.S.A.) will evaluate the effect of β-carotene, vitamin E and aspirin every other day on several chronic disease endpoints, including incident cancers of the lung, colon and breast, in female health professionals 45 years of age or older. Another trial (Dr R. Sandler, University of North Carolina, U.S.A.) is investigating the effect of aspirin 325 mg daily (versus placebo) on adenoma recurrence and disease-free survival in patients surgically treated for early stage colorectal cancer. Still another intervention study (Dr J. Baron, Dartmouth University, U.S.A.) involves a

comparison of 80 and 325 mg aspirin daily (with and without folate) with placebo in individuals with at least one recently removed adenoma. Adenoma recurrence trials with aspirin and calcium carbonate combinations are currently under consideration.

Ibuprofen. The activity of this compound derives primarily from competitive inhibition of cyclo-oxygenase, although the drug's full effects are incompletely understood. Ibuprofen has shown chemopreventive activity in several animal cancer models, including colon in the rat. Epidemiological studies have shown inverse relationships between non-aspirin NSAID use and colorectal adenomas and cancer. The gastrointestinal toxicity of ibuprofen in humans appears to be less than that of other NSAIDs under consideration as chemopreventive agents.

Piroxicam is a potent inhibitor of cyclo-oxygenase and is, therefore, both a very active and fairly toxic NSAID, at least at doses $\geq$ 20 mg daily. The usefulness of this compound will depend on whether an effective dosing strategy with minimal safety risk can be developed.

Sulindac Sulindac, still another cyclo-oxygenase inhibitor, was discovered in a search for a less toxic version of indomethacin, a structurally related compound. Activity has been demonstrated in several animal studies against inhibition of new carcinoma induction, as well as growth of existing carcinomas, although the effects on proliferation measured in such models have been inconsistent.

To date, three small studies of sulindac therapy for polyps in familial adenomatous polyposis patients have been carried out. These studies have shown reductions in number or size of observed lesions [19]. In individual case studies sulindac has been reported to cause regression of existing polyps and prevention of new ones. In one study, it was reported that polyps largely disappeared on initial sulindac treatment, recurred in some patients after discontinuation of therapy and regressed after reinstitution of treatment. These findings are certainly provocative and justify more definitive studies of this potential chemopreventive agent.

VITAMINS

β-*Carotene*

β-Carotene has been proposed as a chemopreventive agent for several cancer sites, including the large bowel. It has several potential mechanisms, including its role as an antioxidant and free radical/reactive species scavenger, and its metabolism to vitamin A, which influences proliferation and differentiation.

The evidence for a chemopreventive role for β-carotene is weaker for large bowel than for other sites. Greenberg and associates recently reported that β-carotene had no effect on adenoma recurrence in a large ($\approx$750 participants) randomised trial [20]. The Physicians Health Study (C.H. Hennekens, Harvard University, U.S.A.) and Women's Health Study may also yield information on the effect of β-carotene on colorectal cancer.

Vitamin E

Vitamin E, which reacts with a variety of oxyradicals and singlet oxygen, has as one of its main antioxidant functions the prevention of peroxidation of polyunsaturated membrane lipids. Other mechanisms of action pertinent to chemoprevention have been proposed. A few epidemiological studies have now shown an inverse relation between vitamin E intake (particularly supplement use) and colorectal cancer. Controversy exists, however, as to whether pharmacological doses of vitamin E can be of preventive or therapeutic value. The effect may be limited to increasing deficient or marginally normal serum vitamin levels to normal range. There is a suggestion from some epidemiological studies of a synergism between vitamin E and selenium, with the highest cancer risk being observed in persons with low serum vitamin E and low selenium status.

A few animal studies have suggested an inhibiting effect of vitamin E on carcinogen-induced intestinal tumours. Results from human trials, however, have shown little effect to date. The reports by Greenberg and associates [20] and McKeown-Eyssen and associates [21] indicated no impact of vitamin E on polyp recurrence. The Finnish α-Tocopherol/β-Carotene Study, designed with lung cancer as the primary outcome, has so far demonstrated no significant effect of vitamin E on colorectal cancer incidence. The Women's Health Study will also provide information on vitamin E's effect on colorectal neoplasia.

Folic acid

Folic acid, an antioxidant found in a variety of vegetables, has generated considerable interest as a possible colorectal cancer chemopreventive, largely on the basis of recent epidemiological findings of an inverse relation between dietary folate and colorectal malignancies [22]. Folate is being included as a factor in the aspirin–polyp recurrence trial being conducted by Baron and colleagues, and is likely to be examined in other studies as well.

OTHER COMPOUNDS

DFMO

DFMO is a potent, irreversible inhibitor of the activity of ornithine decarboxylase, an enzyme catalysing the conversion of ornithine to putrescine, a key step in the synthesis of polyamines, which are involved in cell proliferation. DFMO has shown activity in azoxymethane (AOM) rodent models, with tumours as well as intermediate markers (proliferation, aberrant crypt foci) as endpoints. DFMO is toxic, effects including loss of hearing acuity (reversible after discontinuation of treatment). Therefore, the identification of an effective dosing regimen with acceptable side-effects in phase II studies will be a criterion for continued development of this agent.

Oltipraz

Oltipraz, a synthetic dithiolthione, is structurally related to naturally occurring dithiolthiones found in cruciferous vegetables which have been shown, in some epidemiological studies, to protect against large bowel cancer. This drug was originally developed as an anti-schistosomial agent. The drug increases GSH (reduced glutathione) levels in rodents in several organs and enhances expression of GSH-S-transferases (GST). The drug inhibited tumour development in AOM rat colon models. An efficacy trial in colorectal cancer is being considered in the next few years.

Ursodeoxycholic acid (UDCA)

UDCA is a minor bile acid found in trace amounts in human and rat bile. UDCA appears to neutralise the harmful effects of other bile acids by inhibiting 7α-dehydroxylase in colonic bacteria, resulting in lower production of deoxycholic acid from primary bile acids, cholic and chenodoxycholic acid. UDCA has been shown in one animal model to reduce the incidence of AOM-induced tumours, and the compound has shown activity

as measured by proliferation and other intermediate markers. UDCA is being investigated in a new, large (about 1000 participants) adenoma recurrence trial (C. Ritenbaugh, University of Arizona, U.S.A.).

DIETARY PREVENTION OF COLORECTAL CANCER

Several lines of ecological evidence are consistent with an important aetiological role for dietary factors in colorectal cancer [23].

Geographical variation in colorectal cancer rates—there is over a 10-fold variation in rates of colorectal cancer between countries with the highest and those with the lowest rates.

Time trends—in several countries, colorectal cancer rates have shown a dramatic change over time. Age-adjusted incidence rates for colon cancer in Shanghai, China increased 75% from 1972 to 1989. In Japan, colon cancer mortality rates increased 44% for men and 40% for women from 1969 to 1981.

Migration—numerous migration studies have demonstrated that rates of colorectal cancer in migrants show a convergence from rates in the country of origin to those in the country of destination, even when rates in the country of origin were higher than those in the country of destination.

Dietary factors are certainly compatible with these ecological findings, given that diet varies markedly from country to country, has changed substantially in those countries in which there have been rapid changes in colorectal cancer rates over time, and clearly changes with migration and acculturation. Moreover, food and food metabolites not only come into direct contact with the mucosa of the large bowel, but also affect several physiological metabolic parameters (bile acid production, short chain fatty acid production and intraluminal pH, for example) that may be involved in neoplastic processes in the large intestine.

It follows that dietary modification may well reduce the incidence of colorectal cancer. Epidemiological, clinical nutrition and laboratory investigations over several decades have identified and examined several major hypotheses on the relation of diet to colorectal cancer.

Nutrient- and chemical-based hypotheses

These include: antioxidant and other micronutrient hypotheses, for example, the possible protective action of vitamin E, calcium and folic acid, discussed above; hypotheses implicating various macronutrients—dietary fat has long been hypothesised to increase large bowel cancer risk, whereas dietary fibre has been proposed to be protective [24]; and the food mutagen hypothesis (heterocyclic amines, produced in high-temperature cooking of meats, have been suggested as factors in the genesis of large bowel malignancies [25]).

Food- and cuisine-based hypotheses

These include foods and food groups—several hypotheses on the relationship of various foods and food groups to cancer are under investigation. Red meat consumption, for example, has been linked to large bowel cancer [26]. Many studies have suggested a protective effect of vegetable and fruit intake on this malignancy, and there are hypotheses concerning dietary patterns ("cuisines")—some have argued that a vegetarian diet can reduce risk of large bowel and other cancers [27]. It has been hypothesised that an overall low-fat, high-fibre, high-vegetable and fruit eating plan reduces the risk of colorectal malignancies, as compared with the more typical "Western" high-fat, low-fibre, low vegetable and fruit fare [28]. In a similar vein, Mediterranean and Asian cuisines, as opposed to U.S.A. or Western European cuisines, might protect against the disease [27].

Several large studies have been initiated around the world to evaluate whether dietary modification can truly affect colorectal carcinogenesis.

FIBRE SUPPLEMENT STUDIES OF ADENOMA RECURRENCE

DeCosse and coworkers conducted a small fibre and vitamin supplement trial in patients with familial adenomatous polyposis [29]. 62 patients were randomly assigned to one of three treatment groups: total fibre intake of 22.4 g/day plus vitamin C (4 g/day) and vitamin E (400 mg/day) (high-fibre group); total fibre intake of 11.3 g/day plus vitamin C (4 g/day) and vitamin E (400 mg/day) (vitamin group); and total fibre intake of 12.2 g/day plus placebo (control group). The first group received a high-grain fibre supplement, the other two groups a low-fibre "placebo" supplement. No statistically significant reduction in adenoma recurrence was observed in the high-fibre group compared to the other groups (intention-to-treat analysis). Because of a decline in adherence during the course of the trial, the authors analysed recurrence data, taking into account actual amounts of fibre ingested. The results adjusted for adherence suggested some reduction in adenoma recurrence in the high-fibre group but, as the authors indicate, this finding was potentially subject to bias introduced by participant or dietary factors associated with adherence.

Ritenbaugh and colleagues are currently conducting an intervention study of the effect of a wheat-bran supplement (13.5 g/day) on adenoma recurrence among approximately 1400 men and women in Arizona, U.S.A. The follow-up period is scheduled to conclude in 1998.

The European Cancer Prevention Organization (ECP) is carrying out a multicentre multinational adenoma recurrence trial among some 800 individuals. The intervention agents, selected because of their putative efficacy in blocking epithelial cell damage from intraluminal bile acids, are calcium (2 g/day as calcium gluconolactate) and fibre (ispaghula husk 3–8 g/day) as the interventions. A unique dimension of the ECP study is its capacity to observe the effects of the intervention agents on small polyp progression, as not all small colorectal lesions will be initially removed.

ADENOMA RECURRENCE STUDIES INVOLVING DIETARY MODIFICATION (WITH OR WITHOUT SUPPLEMENTS)

Canadian study

McKeown-Eyssen and colleagues have recently reported the results of a small diet–adenoma recurrence trial conducted in Canada [30]. After removal of one or more colorectal adenomas, 201 men and women were randomised to receive counselling on a low-fat (either less than 50 g/day 20% energy), high-fibre (50 g/day) diet or follow the customary Western diet (high in fat, low in fibre). (The control group also received a "placebo" fibre supplement containing 3 g of dietary fibre in a 50 g package.) After 1 year of counselling, fat intake was 25 and 33% of total energy, respectively, in the intervention and control groups; fibre consumption was, respectively, 35 and 16 g. A relative risk of 1.2 (95% confidence interval (CI), 0.6–2.2) for adenoma recurrence in the intervention compared to the treatment group was observed after an average of 2 years observation of 165 participants, who had the follow-up colonos-

copy (intention-to-treat). This implies no overall statistical difference in adenoma recurrence between the two groups.

The relative risks in the intention-to-treat analysis of data from the Canadian study were 1.6 (95% CI 0.7–3.6) for men and 0.7 (95% CI 0.3–2.0) for women. An "exploratory analysis" of 142 men and women counselled for at least two-thirds of the period between initial dietary counselling and follow-up colonoscopy yielded relative risks of 1.9 (95% CI 0.8–4.4) for men and 0.5 (95% CI 0.1–2.1) for women. Of note is the finding that these gender-specific relative risks were associated with bile acid excretion: male intervention group participants excreted greater concentrations of faecal bile acids compared to controls, while female participants excreted lower concentrations. Although these gender-specific differences are intriguing, overall this was a null study. Because of the small sample size, the confidence intervals (for men and women separately and combined) indicate that the results are compatible with protective, null and even harmful effects of dietary modification on adenoma recurrence.

Australian Polyp Prevention Project

This recently completed trial employed three interventions in a 2×2×2 factorial design [31]. These were a low-fat diet (≤ 25% calories from fat), a 25 g wheat bran supplement and 20 mg of β-carotene. Colonoscopies to ascertain adenoma recurrence were performed after 2 and 4 years of follow-up. Four hundred and twenty four participants were randomised into this trial.

Adenoma recurrence was slightly (but not significantly) increased in the group receiving β-carotene (intention-to-treat). There was a slight, non-significant reduction in all recurrent adenomas among participants in the low-fat group. The number of large (≥ 1 cm) adenomas, however, was 70% lower in the low-fat group (relative risk (RR)=0.3, 95% CI 0.1–0.9). Among participants in the wheat bran supplement group, there was a small non-significant increase in adenoma recurrence for all adenomas, and a slight non-significant decrease for large adenomas. No subjects on the combination of low-fat and wheat bran diet developed large adenomas over the 4 years of follow-up ($P<0.01$).

The investigators conclude that the low-fat diet reduced the recurrence of large adenomas, and suggest an effect enhanced by the addition of wheat bran to the low-fat diet. They argue that inferences to large bowel cancer may be stronger for findings on large, as opposed to all, recurrent adenomas. Alternatively, dietary factors may preferentially inhibit faster growing neoplastic lesions. It should be noted, however, that the preliminary findings indicate that the study was null for overall adenoma recurrence, the primary endpoint.

Polyp Prevention Trial (PPT)

The National Cancer Institute is currently conducting a multicentre, randomised, controlled trial evaluating the effect of a low-fat, high-fibre, high fruit and vegetable dietary pattern on large bowel adenoma recurrence. The large sample size ($n=2079$) permits the detection with over 90% power of a reduction of 24% in the polyp recurrence rate. The PPT involves a comprehensive, multifactorial eating plan rather than an intervention based on supplements or a single dietary factor. PPT intervention group participants are counselled to change their overall dietary pattern by meeting three goals: 20% of calories from fat, 18 g fibre/1000 kcal, and five to eight servings of fruits and vegetables (the exact number based on caloric intake). Repeat colonoscopies are carried out at 1 and 4 years follow-up. Recruitment for this study was completed in early 1994, with the last completion of study procedures anticipated in early 1998.

THE WOMEN'S HEALTH INITIATIVE: A DIETARY INTERVENTION STUDY WITH COLORECTAL CANCER AS AN ENDPOINT

The Women's Health Initiative, a very large, ambitious NIH-sponsored study of heart disease, cancer and osteoporosis in women in the U.S.A., will include a dietary intervention study that has colorectal cancer incidence as one of its evaluable endpoints. The randomised controlled clinical trial component of the study will enrol approximately 60 000 postmenopausal women between the ages of 50 to 79 years of age. The trial has three interventions, although women can choose to be randomised into two or three of the overlapping studies. The interventions include a low-fat eating plan (with explicit emphasis on increasing consumption of fruits and vegetables), hormone replacement therapy and calcium/vitamin D supplementation. Forty-eight thousand women will be randomised into the dietary component of the study (19 200 in the intervention arm, 28 800 in the control arm). 4 years for protocol development and 9 years of follow-up are planned. The trial has approximately 90% power to detect a reduction of 20% in the incidence of colorectal cancer.

CONCLUSION

As yet, we have no definitive proof that it is possible to prevent colorectal cancer, but the chemo- and dietary prevention strategies have real promise. We now await the results of the several large-scale trials underway around the world. The findings from these intervention studies may provide evidence to transform promise into reality.

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