Can Dietary and Pharmacological Supplements Prevent Colorectal Cancer?

Prevention of colorectal cancer, by adding a dietary or pharmacological product to the “western” diet, is being actively researched. The natural dietary constituents, such as fiber, calcium, and folic acid have been shown by epidemiological and experimental studies to be useful in preventing neoplasia, but have minor protective effects when used as short-term dietary supplements. The most useful chemopreventive agents already available are aspirin, selective cyclooxygenase-2 inhibitors and now, nitric oxide-aspirin. Each having decreasing less toxicity, but the newer drugs are still being evaluated in clinical trials. A life-long well-balanced diet, rich with dietary sources of fiber, vitamins and minerals, and healthy lifestyle, are probable the most cost-effective means to reduce the risk for colorectal neoplasia. Chemoprevention with medications is still unproven, expensive and with some toxicity. Screening is the immediate means to reduce mortality and morbidity from colorectal cancer.

For some time, there has been an effort made to identify and evaluate dietary components and chemical compounds (chemopreventive agents) that could prevent, inhibit or change the course of colorectal (CR) carcinogenesis (1). These efforts were based on clinical and lay observations, beliefs and epidemiological correlations, that certain foods or additives had beneficial anti-carcinogenic properties. These include natural constituents of foods, e.g. vitamins and minerals; medications, e.g. aspirin, that have non-chemopreventive attributes; chemicals derived from foods and believed to have anticarcinogenic properties; chemicals promoted for their anti-carcinogenic properties, e.g. COX-2 inhibitors.

The sites of action and mechanisms of chemoprevention are numerous and vary from agent to agent (1) (Table 1 and Figure 1). Once an agent has been identified as possibly having anticancer properties, it is usually evaluated in an animal model, which is often

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animal model are useful, then short-term studies are performed in humans, looking at “intermediate biomarkers” of response to the chemopreventive agent (Table 2). Next, a clinical trial is performed in persons at risk for developing adenomatous polyps, e.g. familial adenomatous polyposis or recurrent adenomas. Randomized, placebo trials in persons at risk of having recurrent, sporadic, adenomatous polyps are usually the last stage, as it would take a too long, large and costly study to evaluate each compound for its anti-colorectal cancer (CRC) effect (1).

This review will briefly refer to some of the agents that have been or, are being evaluated clinically and could, or have already, reached clinical application. A more detailed description can be found in reference 1 which is extensively quoted with permission of the publishers and authors. For the sake of brevity, older references are not quoted as they appear in reference 1.

**DIETARY AGENTS**

**Fiber**

Large, prospective, observational studies in the USA and Scandinavia did not show a CRC protective effect of dietary fiber, nor were CRC death rates decreased in vegetarians (2–5). However, these studies had mostly been performed in single populations having almost homogeneous diets. In a recent, large, CRC screening study, dietary fiber was found protective for distal adenoma;
3,500 persons from diverse areas of USA, out of 56,000 undergoing sigmoidoscopy, had adenomas detected. After risk factors adjustment, those having the highest intake of fiber had 27% fewer adenomas (P < 0.01). The strongest protection was from grains and fruits; the results were similar for both sexes and for “advanced” and non-advanced adenoma (6).

The large European, multi-national, EPIC study, evaluated dietary fiber intake and CRC incidence 1992–98, in 520,000 persons from 10 countries, having diverse diets, food sources and intake of fiber. The adjusted CRC relative risk with highest fiber intake, was 0.58 and the protective effect was greatest for the left colon and independent of fiber source (cereals, vegetables, legumes or fruits) (7).

In contrast to the overall conclusion that an adequate long-term intake of dietary fiber has a role to play in preventing large bowel neoplasia, the beneficial effects of short-term fiber supplements is less well established. This had been evaluated in studies looking at the effects of fiber on large bowel epithelial proliferation, and/or adenoma recurrence. Large intervention trials with bran, soluble fiber or vegetables did not always reduce adenoma recurrence. In a multinational European trial, giving supplemental soluble fiber (3.5 g/d ispaghula) for 3y, to post-polypectomy patients, actually led to increased adenoma recurrence (8). In an Australian trial, a low fat (25% calories) and 25 g/d wheat bran diet for 2–4y, significantly reduced the risk for recurrent adenoma, but only for those that were >1 cm (9). Supplements for 3y of 13.5 g or 2 g of wheat bran, did not protect against recurrent adenoma; nor did a 4y diet with high fiber, fruit and vegetables and low in fat reduce adenoma recurrence (10,11). So, the effect of fiber, if beneficial, is not prominent and apparently is dependent on the total diet constituents eaten and their interactions. For example, in a study of long-term diet, those persons have the highest intake of fiber and water had the lowest risk for adenoma (1,12,13).

In conclusion, observational studies of diverse populations demonstrated a reduced risk for adenoma or CRC in those persons having the highest dietary fiber intake. This is true for men and women, was least for rectal neoplasia, and was independent of fiber sources but greatest for grains and fruits. Intervention studies for 2–4y, with fiber and/or other dietary changes, did not usually reduce the adenoma recurrence rate. A life-long, high-fiber diet (grains, fruits, vegetables) is probably protective, while short-term fiber supplements are not very effective.

**Calcium**

This dietary constituent has been investigated epidemiologically, experimentally and clinically for its anti-CRC properties. The most impressive evidence for this is experimental, e.g. by giving a “western-style” diet to mice and suppressing the resulting hyper-proliferative response of the mouse colonic epithelium by adding dietary calcium (1). The epidemiological evidence is not supportive for a strong anti-carcinogenic role, but rather for a modulating, protective role within a “carcinogenic” western diet. In adenoma patients suppression of rectal epithelial proliferation by long-term calcium dietary supplements is greatest when their dietary intake is high in carbohydrate, fiber, and water and low in fat and tobacco use (1).

The strongest evidence for the chemopreventive use of calcium comes from the trial by Baron et al., giving calcium or placebo for four years to adenomatous polyp patients (1). The intervened group had a small, but significantly reduced risk for adenomatous polyp recurrence. The daily dosage given, of 3 g of calcium carbonate, added 1,200 mg of calcium ion to the daily intake of dietary calcium. Other studies used 1,500 mg of calcium ion per day. The sources of calcium used, and whether they were insoluble or soluble salts were not important and different compounds gave similar results. Only about 30%–40% of ingested calcium is absorbed and the remainder reaches the large bowel, mixed with the intestinal contents, makes some contact with the mucosa, and finally, is lost in the stools. So, 4 to 6 300 mg calcium carbonate tablets/d is a dosage proven to suppress the risk for colorectal neoplasia in persons having had an adenomatous polyp, and, or, large bowel epithelial proliferation in persons having had an adenoma or family history of colorectal cancer (1). But, no such neoplasia-prevention studies have been performed in the average-risk population.

The source of calcium ingested is less important, but rather its total intake of up to 1,500–2,000 mg cal-

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cium ion/d. The dietary reference intake of calcium for adults aged 50y or older has recently been increased to 1,200 mg/d (1). This latter value probably reflects the minimal physiological needs and the former, the pharmacological effects. Very few adults have this minimal intake when eating their “western” diet (1). A higher calcium intake is best obtained from a diet rich in calcium, such as calcium-containing low-fat milk products. This diet is practical in volunteers and suppresses their large bowel epithelial proliferation (1). However, it has not been proven to prevent CR neoplasia, nor is its long-term effects known. Because of the increasing evidence supporting the effect of calcium in preventing CR neoplasia and other common disorders in high-risk persons, there is more interest to supplement diets with calcium. There are low-fat, high-calcium, dairy and breakfast-food products that are being marketed for the prevention of osteoporosis.

In conclusion, calcium probably has only a minor, modulating effect, between protective and aggressive dietary factors, in preventing CR neoplasia, with a maximum effect in persons having a calcium deficient diet. This is also probably true for chemoprevention with other natural food constituents. Calcium should be given with suitable dietary counseling so as to provide a well-balanced diet (1). Contraindications to giving calcium supplements or for increasing the dietary calcium intake include hypercalcemia, nephrolithiasis, renal insufficiency and intolerance to treatment.

Vitamins-Folic Acid

Folic acid is important for methylation, which helps maintain genetic stability (1). In humans, there is some epidemiological evidence that CR adenomas and cancers were more common in persons having a low folate intake, while conversely the lowest risk was in persons having a high folate intake (1). Significantly less CRC occurred in those of 89,000 nurses having the highest dietary multivitamin folate intake over 15y (1). In another study, CRC and adenoma patients were found to have had a lower folate intake, lower blood folate and $B_{12}$ levels, and colonic DNA hypomethylation, while conversely, a higher folate status was associated with decreasing CR neoplasia risk (14). Elderly men with low folic acid, but a high alcohol intake and the $MT_HFR$ Val/Val genotype (which limits folic acid utilization) were seen to have an increased risk for CRC (15). There are no completed folic acid intervention studies.

Bioactive Drugs

These are purified, active substances, found in fruits, vegetables, cereals and spices, e.g. green tea or soya beans, and believed to have anticancer properties. The evidence for their usefulness was initially based on local beliefs, clinical impression and some epidemiological evidence. Even when their effects have been demonstrated experimentally, it is unlikely that their occasional ingestion in a mixed western diet is useful. However, there are some national groups or individuals where their consistent intake may have a significant contribution as anti-carcinogens, e.g. green tea, curry, etc. (1). The long-term ingestion of isoflavonoids and lignans, found in soya beans and rye cereal, has been associated with a lower risk of cancer, especially breast and prostate cancer, in Asia and Scandinavia (1). Their effect in preventing CRC is less established (1). Genistein is a popular nutritional supplement and has a molecular structure similar to estrogen, and therefore termed a phyto-estrogen. Its modes of action are multiple and include inhibition of proliferation, promotion of apoptosis and inhibition of angiogenesis in experimental studies, as well as its anti-estrogen effect. The epidemiological evidence for its preventing CRC is not as convincing as for the hormone-dependent neoplasia (1).

In conclusion, fruits, vegetables, spices, etc. contain a number of potent anti-carcinogens, probably acting together at different stages of carcinogenesis (Figure 1). Their protective effect being greatest when given to persons having the lowest level of consumption (16).

PHARMACEUTICAL AGENTS
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Aspirin

The strongest epidemiologic evidence for an effect of medications in preventing CRC is for the NSAIDs family in general, and specifically for aspirin (1,17).
The clinical evidence is for a 50% reduction in incidence of large bowel cancer in chronic users (18). It has also been noted that aspirin interacts with diet to reduce CRC risk (19). Results of intervention trials with aspirin on adenoma recurrence are available now.

The relative risk of adenoma recurrence in 517 patients receiving 325 mg/d aspirin for 13m was 0.65 (20). While the relative risk of developing an advanced adenoma in 1,121 patients after 81 mg/d aspirin for 12m, was 0.6 (21). But, CRC incidence was not reduced in 29,500 persons receiving 150 mg/d aspirin for 9y (22). So, low-dose aspirin is probably not CRC protective. It is still not clear what dosage of aspirin is needed for preventing colorectal neoplasia, and for how many years it should be given before its benefit is obtained (1). In addition, what are the side effects (such as gastrointestinal bleeding) that can be expected vs. the benefit in reducing the likelihood of dying from CRC? This is a concern in the elderly-aged, who are often taking multiple medications for a variety of disorders (1). In an editorial, Imperiale wrote that the “cumulative risk of major adverse effects most likely outweighs any benefit in prevention...”; “saves fewer lives at higher cost than does screening” (23).

**Selective COX-2 Inhibitors**

Cyclooxygenase 1 (COX-1) is a physiologically important enzyme needed for the synthesis of prostaglandins, and is found in the kidney, brain and gastrointestinal mucosa where it has a cytoprotective function. COX-2 is induced during inflammatory processes, cellular proliferation and progression to neoplasia. Aspirin and the other commonly used NSAIDs, while aiming at COX-2, have a non-specific effect and inhibit both COX-1 and 2 (1). This non-specific inhibition can result in the loss of cytoprotection and allows for damage to occur to the gastro-duodenal mucosa. So, studies are being carried out with specific COX-2 inhibitors and, or, promoters of apoptosis and inhibitors of invasiveness and angiogenesis, which may provide a better complication-benefit ratio than that obtained with aspirin (1). New NSAIDs that are COX-1 sparing and are COX-2 specific inhibiting medications, have been developed and marketed (1). The highly specific COX-2 inhibitors include celecoxib (Celebrex™, Searle, U.S.) and rofecoxib (Vioxx™, Merk, U.S.). So far, none of these have been approved for preventing sporadic colorectal neoplasia, but trials are in progress. The US Food and Drug Administration approved Celecoxib as an adjunct therapy in Familial Adenomatous Polyposis (FAP). This is based on good clinical evidence that non-COX specific NSAIDs, such as sulindac will inhibit the growth of adenomatous polyps in the retained rectum of FAP patients, and this was confirmed in a trial using Celecoxib (1) (Figure 2). Unfortunately, this is an incomplete therapeutic effect as intramucosal adenomatous tissue remains present and CRC can occasionally occur even while under treatment (1). So, in an ongoing genetic disorder such as FAP, it is very unlikely to (continued on page 25)
obtain a complete therapeutic effect. The high dosage needed, and subsequent costs are considerable. There is much less gastric damage than from aspirin, but there are dose-dependent side effects: some nephrotoxicity, rise in systolic BP, and edema (24). In addition, COX-2 inhibitors lack the anti-platelet and cardioprotective effect of aspirin. For the average and high-risk for CRC persons, this chemoprevention is more costly than CR screening alone or when given in addition to screening (25).

**Nitric Oxide-releasing NSAIDS**

These new compounds are more effective and efficient in suppressing cancer cell growth by inhibiting proliferation, inducing apoptosis and blocking the cell cycle synthetic phase. They do not stop prostaglandin synthesis or act via COX enzymes (26). There is less gastric toxicity than with aspirin as they increase the mucosal blood flow, mucous release and mucosa repair, and inhibit neutrophil activation and adherence.

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These drugs have been evaluated in animals and in short-term human studies, but there are no results from intervention studies (27).

**Post-menopausal Hormones**

Meta-analyses of large, follow-up studies in treated women, point to a CRC protective effect of estrogen replacement therapy, with or without progesterone (1).
The prospective studies support a protective effect, although small and possibly transient. This is consistent with the observation that CRC is slightly less common in pre-menopausal women than in men, and that the rates rise in the post-menopausal women.

**HIGH-RISK PATIENTS**

**Familial Adenomatous Polyposis (FAP)**

The recommendation is to maintain a “balanced” diet/lifestyle. In the Apc mutation mouse model, caloric restriction or diet supplemented with olive oil, fruits and vegetables significantly reduce the number of polyps (28). In the human with FAP, celecoxib is given to delay elective surgery, while celecoxib or sulindac orally or an intra-rectal NSAID (for rectal polyps) have been given to reduce the number of polyps in the retained rectum and before definitive surgery (1).

**Hereditary Non-Polyposis Cancer (HNPCC) and Non-adenomatous Polyps**

HNPCC “knock-out mice” have tumorigenesis inhibited by adding dietary calcium or vitamin D (personal communication, Dr Lipkin, New York). COX-2 is found in polyp mucosa, fibroblasts and endothelium; but is also 50-fold more produced by HNPCC fibroblast cell lines as compared to that of sporadic CRC fibroblasts (29). So, COX-2 inhibitors not only suppress growth of sporadic adenomas, but might also be useful for non-adenomatous polyps and HNPCC (30).

**Ulcerative Colitis (UC)**

It was observed that ulcerative colitis patients, who often have a low vegetable and fruit intake and if taking salazopyrine (a medication known to interfere with folic acid metabolism), were more likely to develop CRC (1). A retrospective study of taking folic acid supplements demonstrated a reduced risk for dysplasia in these patients (1). Even so, there are no published large-scale chemopreventive studies in ulcerative colitis patients that prove its anti-cancer usefulness. Treatment of primary sclerosing cholangitis with ursodeoxycholic acid significantly reduces the incidence of CRC/dysplasia in UC patients (1,31,32).

**WHICH DIETARY OR CHEMOPREVENTIVE AGENT TO CHOOSE?**

The agent needs to be a medication or food additive taken long term, having no significant side effects and having clinically proven cancer preventive properties (Tables 3 and 4). An analysis of chemopreventive trials in animal models and adenoma recurrence in humans has recently been published and also given in more detail on http://www.inra.fr/reseau-nacre/sci-memb/corpet/indexan.html (33).

From the list of medications, the new COX-2 inhibitor medications seem most useful. However, long-term studies are still needed for them to be proven effective in CRC prevention. Recently, there has been a suggestion that their therapeutic benefit may be improved by low-dosage combination therapy with drugs acting through different, but complementary pathways (34). It is very likely that initially persons at increased risk for CRC will use them, and they include persons with a marked family history of CRC or personal history of adenoma. For women, the decision to take post-menopausal replacement hormones is individual and the side effects and long-term risks for other malignancies need to be considered. If taken, then the risk for large bowel cancer is slightly reduced.

Based on the evidence from populations having a high consumption of soya and green tea, their active principles are worthy of further studies in humans at risk for CRC. In the meantime, calcium enriched foods would seem to be useful, at a minimal risk for side effects and costs.

**CONCLUSIONS**

Lifelong, preventive dietary and lifestyle habits are the best and most economic means to diminish the occurrence of CRC. However, this is not implemented in the “westernized” world. Chemoprevention with natural food constituents is probably useful for those having an unbalanced/deficient diet. Chemoprevention with drugs may be useful, but at a cost—both financial and
with side effects. Today, screening is feasible and an immediate answer to reducing the mortality from CRC in most high-risk countries.

References