Primary prevention of colorectal cancer

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Introduction

Colorectal adenocarcinoma is the second most common cancer in the industrialised countries. In Belgium, more than 6000 new cases are diagnosed every year, among whom more than 50% will die of the disease (1), despite constant progress in treatment modalities, including surgery, radiation therapy or chemotherapy. Colon cancers arise as a result of a series of pathologic and molecular changes, which transform the normal cell into a cancerous cell, with an adenomatous polyp as an intermediate step in most cases. Necropsy data reveal that adenomatous polyps are as frequent as 50 percent in the general population by the age of 70 (2).

Substantial progress is expected from prevention, which is generally divided into primary and secondary prevention. Secondary prevention deals with early detection and screening, and polyp removal. Primary prevention consists in identifying modulating factors and providing populations with advises and recommendations, or interventions with chemoprevention. It is a wide and promising field, with considerable benefit to be expected. For example, a 1% decrease in cancer incidence in the USA (more than 100.000 new cases per year, more than 50.000 deaths) would spare 500 lives per year.

Inherited susceptibility factors may be important in most cases of colon cancer. There are well-established inheritable syndromes, which account for about 6% of the incidence, 1% for familial polyposis syndromes and 5% for the hereditary non polyposis colorectal cancer, or HNPCC (3). The other 94% are considered "sporadic". Hereditary factors play a significant role in these as well : first-degree relatives of individuals with colorectal cancer or adenomas carry a 3 to 4 times increased susceptibility to develop cancer (3) But other factors must be considered to explain the wide variety of incidence around the world. Incidence rates are typically higher in the most "westernised" than in underdeveloped countries, with a variation reaching a 1 to 30 range. It was a relatively infrequent cancer in the nineteenth century, but its incidence in the United States and Western Europe has been constantly rising since then, even if a trend to some decrease is appearing in the nineties.

Environmental factors account for the major influence on colon cancer incidence. This was first suggested by migration studies, which showed that people who move from a low risk country to a high risk country (e.g. Japan to Hawaii) share the same increased risk of the new country after one or two generations (4). Among these environmental factors, diet appears to have the main influence. The populations who demonstrate a high risk are characterised by a so-called "Western diet", with a high fat - low fiber intake. In the European Union, there is a clear trend between the northern countries, e.g. Germany, England or Belgium, with a higher than average risk, and the Mediterranean countries, e.g. Spain, Portugal or Italy, with a lower risk, and a higher-vegetable and fruit, lower-meat diet.

Besides these two major dietary factors, fat and fiber, several other micronutrients have been proposed as chemopreventive agents, such as calcium, vitamin D, ascorbic acid, selenium, retinoids, tocopherols, folate or methionine. More recently, the potential role of nonsteroidal anti-inflammatory drugs in chemoprevention has raised a lot of interest. Table 1 summarises the constantly expanding list of potential risk modulators, either protective or deleterious, with more or less experimental evidence. This article reviews the most frequently mentioned in the literature, with often more controversy than consensus.

Aims and methods of primary prevention

Primary prevention of colorectal cancer aims at reducing its incidence at three levels : firstly identifying the risk factors of cancer, then understanding their

Table 1. — **Potential modulators of the risk of colorectal cancer**

Protective	Deleterious
Fiber	Fat
Calcium	Calories
Vitamin D	Sugar
Ascorbic acid	
Selenium	
Retinoids	
Tocopherols	
Folate	
Butyrate	
Methionine	
Exercise	
Estrogens	
NSAIDs	

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mechanisms of action, and finally modulating their influence at the population level by intervention.

Initial evidence usually comes from the epidemiological studies, but their results can be difficult to interpret, or controversial. The effects of dietary factors are usually interrelated, so that the specific action of individual modulators is difficult to isolate, for example fat and fibre. They rely on dietary questionnaires, usually not standardised, and not reproducible from one study to the other. Most of them are retrospective.

Experimental models are mandatory to investigate their mode of action. Animal models have been developed, in which rodents are exposed to specific carcinogens, such as azoxymethane or 1-2 dimethylhydrazine, and subsequently develop colon tumours, either benign or malignant. The influence of individual agents, dietary or chemopreventive, on tumour incidence, size, number and growth can be studied. More recently, a new animal model has been developed, the Multiple Intestinal Neoplasia (MIN) mouse, consisting in genetically manipulated rats, with a heterozygous mutation on the APC gene, leading to early intestinal adenomas and cancer occurrence, without any addition of carcinogen (5). These studies provide useful data, but no conclusion can be drawn, because the animal model do not exactly reproduce the human polyp-cancer sequence, especially in terms of duration and intermediate steps.

Biomarkers of risk are very useful research tools, both to identify groups of population at high risk, and to conduct intervention studies. They consist in intermediate cellular or biological parameters varying in parallel with the risk of developing cancer. Cell proliferation or apoptosis are examples. The proliferative compartment of epithelial cells increases in size in colonic crypts of humans at increased risk for colorectal cancer, and it expands from the bottom to the upper part of the crypt (6). More recently, aberrant crypt foci have been shown to be precursors of adenoma and cancer in humans. They consist of large, thick crypts, which also appear in the carcinogen-treated rodents (7). These biomarkers can be used as an intermediate end point in studies of the action of risk-modulating agents, either *in vivo* or *in vitro*. They provide short term results on small number of subjects, before initiating prospective studies targeting tumour incidence itself as an end point, which require large cohorts and long delays before final results can be brought, and are very expensive. Thus, studies on intermediate endpoints are mandatory before considering them.

Fiber

Among all the agents supposed to exert some protective effect on colorectal cancer risk, fiber, or perhaps more accurately fibers, is probably the most controversial.

Fiber is a concept that include many different substances, mainly polysaccharides, which cannot be absorbed by the digestive tract, but are susceptible to be metabolised by bacteria present in the colonic lumen. It includes cellulose, pectin, lignin, bran,... Burkitt was first to attribute differences in colon cancer incidence between African and Western populations to dietary fiber (8). Since then, a wide number of retrospective epidemiological studies, have suggested a link between dietary fiber and cancer, even if their conclusions may sometimes go to opposite directions. In a vast prospective cohort study among 88,751 nurses aged 34-59 years followed-up as to their risk factors for cancer and coronary heart disease ("Nurse's Health Study"), it was found that a low intake of vegetables and fruits was associated with an increased risk of developing colon cancer, independently of all factors, except meat intake (9). In a case-control study of 170 cases and 7284 controls, Giovannucci *et al.* found that dietary fiber intake was significantly associated with a decreased risk of colonic adenoma (10). A recent meta-analysis of 16 case-control studies provided an estimated combined odds ratio of 0.57 (95% confidence interval = 0.50-0.64) for colon cancer when comparing the highest and lowest quintiles of fiber intake. The odds ratio was 0.48 for vegetable consumption (11). Nonetheless, at least four studies have found no correlation between colon cancer and fiber intake (12). Results in animal studies also tend to support that fiber is protective, even if this conclusion is not always consistent, different types of fiber seeming to affect tumour development in various ways. In general, wheat bran appears to be more effective in tumour inhibition compared with other sources of fiber (13). In a study of 17 patients who had undergone surgery for colon cancer, dietary supplements of wheat bran as 13.5 g/day resulted in a significant decrease in initially high 3H-thymidine labelling indices in rectal mucosal biopsies in most of them, thus indicating a reduction of the proliferation activity of their rectal epithelium to more quiescent values (14). Based upon those results, even in the absence of final conclusions, these findings were considered sufficient to the US National Cancer Institute to propose dietary recommendations in the early eighties, consisting in an increase in dietary fiber from 8-12 to 20-30 g per day, and a reduction of dietary fat below 30% of total calories.

Recently, three prospective randomised studies on the human adenoma recurrence model, have seriously questioned the accuracy of a protective effect of fiber, if any. Alberts and the Phoenix Colon Cancer Prevention Physicians randomly assigned 1429 men and women who had colorectal adenomas removed, to receive dietary supplementation of wheat-bran fiber or low amounts, and showed a similar risk of adenoma recurrence in both groups (multivariate adjusted odds ratio 0.88, 95% confidence interval, 0.70 to 1.11 ; P = 0.28) (15). Schatzkin and the Polyp Prevention Trial Study Group randomly assigned 2079 subjects to follow a low-fat, high-fiber diet rich in fruits and vegetables, or a standard diet, and did not show any difference between

the two groups in terms of adenoma recurrence (unadjusted risk ratio 1.00, 95% confidence interval, 0.90 to 1.12) (16). Even more striking is the European Cancer Prevention Organisation (ECP) intervention study, in which 665 subjects were randomly assigned to receive either fiber supplementation (3.5 g Ispaghula Husk), calcium supplements, or placebo, using a parallel design. It suggested a deleterious effect of fiber (adjusted odds ratio 1.67, 95% confidence interval, 1.01 to 2.76 ; $P < 0.042$), especially in patients with a high dietary calcium intake (17). Moreover, the "Nurses' Health Study", revisited in 1996, failed to show a significant association between fiber intake and the risk of colorectal cancer (18). These observations are considered by some to be comprehensive enough to close the controversy and draw final conclusion that fiber, either dietary or supplemental, is not protective against the development of either colorectal adenomas or colorectal carcinomas (19). However, several comments can be argued before ending discussion. Firstly, the human adenoma recurrence model affects only the growth of small into large adenomas, or large adenomas into carcinomas, which are late stages of colorectal carcinogenesis. Animal studies covering the whole sequence of cancer development suggest that fibers may effect its protective action at earlier stages. We do not know what would be the effect of longer period of intervention, at a younger age, or with other type of dietary modulation, or the role of food processing techniques. Fiber is a very heterogenous group of various compounds, which may have quite different actions, sometimes very difficult to isolate from interference of other dietary factors, such as fat and calories. Several epidemiological studies suggest that the protective action might be correlated with the source of dietary fiber, fruits and vegetables displaying a stronger protection than grain or cereal fibers. Other found that only cereal fiber had a negative correlation with colon cancer mortality (20). Thus, if a protective action of fiber is more than ever questionable, it cannot be totally ruled out at present, and further investigation is still useful.

If fiber is protective against colorectal cancer, it is supposed to act by several possible mechanisms. Firstly, it acts as diluting agent : it increases the faecal bulk, reduces the transit time, binds a wide variety of reactive compounds, thus decreasing the concentration of carcinogens present in the colonic lumen and reducing their contact time to the colonic mucosa. A positive correlation was shown between the dietary intake of non starch polysaccharides and the average stool weight, inversely correlated with the incidence of colorectal cancer (21). Faecal bile acids or salts can be cancer promoters. They have been shown to be more concentrated in the faeces of population with high colorectal cancer, like residents of England or Scotland, compared with those of lower risk, such as Uganda, Japan or India (22). Fiber is able to bind to these compounds, and make them biologically inert or inactivated, by its modifying action on the intestinal flora. Fiber is metabolised by the intestinal flora, with subsequent increase of the production of short chain fatty acids, acetic, propionic and butyric. Butyrate has been shown to induce apoptosis, stimulate differentiation and regulate the expression of some oncogenes, which may account for its protective role. It also acidifies the stools, a lower faecal pH characterizing lower risk population, like African-Americans compared with White higher risk groups (22). Fiber may also induce functional and structural changes in gut mucosa, including direct action on proliferation and apoptosis. However, the actual influence of these mechanisms in humans still remains to be demonstrated.

Dietary fat

The realisation that dietary fat in excess, mostly of animal origin, was a health problem began in the 1960's, initially in the causation of coronary heart disease, and it was soon associated with cancers of the colon, the breast and also the endometrium and the prostate. Most epidemiological studies, although not all, show or at least suggest a positive correlation between rhe risk for colorectal cancer and fat intake, mostly animal fat and meat. The "Nurses' Health Study" supported this suggestion and provided an estimated combined odds ratio of 1.89 (95% confidence interval = 1.13 to 3.15) for colon cancer when comparing the highest and lowest quintiles of animal fat intake. After adjustment for total energy intake, the relative risk of women consuming beef, pork or lamb as a main dish every day is 2.49, when compared with those who consume it less than once a month (9). The ratio of the intake of red meat to the intake of chicken was particularly strongly associated with an increase of colon cancer (9). Different types and amounts of fat exert different actions, sometimes in totally opposite directions. Saturated fat appears to play the major role in increasing risk. This is widely supported by either epidemiological studies, or studies using the carcinogen-treated rodent model. High levels of dietary fat results in a higher level of induced cancers (23). But the situation is not as simple as that. Animal studies have shown that the incidence of colon tumours was significantly reduced in animal fed diets high in omega-3 and omega-6 polyunsaturated fatty acids (24). These findings are supported by the observation of a lower cancer incidence in Mediterranean countries and Eskimo populations, whose main fat supply consists in olive oil, monounsaturated fatty acid or fish oil, containing mostly omega-3 fatty acids. Thus, in the future, we should not talk about dietary fat as a whole, but clearly separate different types of fatty acids.

Different potential mechanisms of action are implicated in the reduction of risk. Long chain unsaturated fatty acids, linoleic, palmitic may act as tumour promoters. A high intake of saturated fat has been shown to increase tumour development in the animal carcinogen-induced colon cancer model (23). They may affect the

proliferation of certain species of intestinal flora, and increase colonic bacteria with a higher enzymatic capacity for transforming bile acids into potential carcinogens, especially secondary bile acids such as deoxycholic or linoleic acids. High faecal concentrations of bile acids are found in populations with high incidence of colorectal cancer (25). In animal models, bile acids act as tumour promoters, perhaps by increasing cell proliferation. The promoting effect of bile acids is increased after enzymatic modification by intestinal flora (26). A reduction of the intake of beef fat has decreased the activity of these enzymes in humans.

Calcium

The first evidence that calcium may exert a protective action on the risk of colorectal cancer came from Garland's 19-year prospective study of a cohort of 1,965 American men, which shown an inverse relationship between the consumption of calcium and vitamin D3, and colon cancer risk (27). Since then, many cohort or case control studies, but not all, have provided the same results. A daily intake above 1,200 mg daily appears to determine a positive influence on the risk of developing cancer (28). Another study showed that a daily intake of at least 150 I.U. of vitamin D provided a 50% reduction rate of the colon cancer risk (27). Although firm conclusions are difficult to draw from these studies, because several confounding values such as fat or total calorie intake were not adjusted, they were the base line to justify further exploration of the potential role of calcium in chemoprevention. Lipkin and Newmark were first to investigate the action of calcium on the 3H-thymidine uptake of the colonic mucosa in subjects at high risk of developing colorectal cancer (29). We treated 9 high risk patients with daily supplementation of 1500 mg of calcium carbonate for 4-8 weeks. Their colonic epithelial cells exhibited a significant decrease of their 3H-thymidine labelling indices in tissue culture. The same decrease of proliferation was obtained when their colon epithelial cells were cultured *in vitro* with high level of calcium (30). This growth inhibition was not observed on 2 adenomas and 2 carcinomas cultured in the same conditions, suggesting that this effect is lost at a stage in tumour development before cells become malignant (30). Many studies have been performed in rodent models, in which calcium has been shown to decrease hyperproliferation induced by several factors, such as bile acids or fatty acids (31). Several studies have reported the protective effect of calcium against carcinogen-induced colon cancer in rodent as well (32).

The results of epidemiological studies have often been inconsistent. Nevertheless, two recent human placebo-controlled randomised studies have shown that calcium supplementation is associated with some reduction in the risk of colorectal cancer. In the Calcium Polyp Prevention Study Group trial, in 832 subjects analysed, the adjusted risk ratio for recurrence of adenoma with calcium as compared with placebo was 0.81 (95 percent confidence interval, 0.67 to 0.99 ; P=0.04), with a lower average number of adenomas in the calcium group (33). In the ECP calcium-fiber-placebo study, in 552 patients who completed the trial, the adjusted odds ratio was 0.66 (95% confidence interval : 0.38-1.17, p<0.16) for the calcium treatment, compatible with a modest beneficial effect of calcium, although non significant (17). Interestingly, this study suggests that that it may preferentially exert its effects on the formation of adenomas in the right colon, and that it can be particularly beneficial in subjects with a low baseline intake of calcium.

Several possible physiological mechanisms have been proposed. Calcium may have a direct effect at the cellular level, by slowing cell proliferation and inducing differentiation. It may also have an indirect action by detoxifying tumour promoters present in the stools, such as long chain free fatty acids or biliary acids, by forming insoluble calcium salts or soaps (34). By binding them, their proliferative and carcinogenic effects are inhibited.

Thus, there is some evidence that calcium may exert at least some chemopreventive effect against colorectal cancer, even if no final conclusion can be drawn at present. We still need more information about effects on actual cancer or later stages of colorectal carcinogenesis than the adenoma, before general recommendations can be proposed. Anyway, calcium is a simple and inexpensive agent, with minimal toxicity, and other potential benefits exist, e.g. a reduced risk of osteoporosis. Altogether, if its protective effect came to be confirmed, calcium might deserve a brilliant future in the field of colorectal cancer chemoprevention.

Folate

Several cohort and case-control studies have found a lower incidence of colorectal cancer in the groups with the highest folate intake. In the "Nurses' Health Study" (9), supplementation with folate was protective against colorectal cancer, although it was usually combined with other vitamin supplementation. This reduction was only confirmed after 15 years of use, which suggests that folate might act early in colon carcinogenesis. Folate is a micronutrient found in great amount in fruits and vegetables, which are supposed to reduce colorectal cancer risk, as suggested by epidemiological studies.

Energy balance and exercise

Regular, moderate exercise has been observed to lower colon cancer risk in several case-control or cohort studies (35). The same kind of risk modulation, either reduction by exercise or enhancement by lack of exercise, has been proposed for several other cancers, including lung, pancreas, prostate, breast or endometrium

malignancies. Animal studies showed that rats with free access to a wheel cage compared with sedentary controls, had a lower incidence of chemically induced mammary gland and colon cancers (36). More than ever, physical exercise appears to be a risk factor very difficult to isolate from other potential modulators. The Western lifestyle, associated with a higher incidence of colorectal cancer, includes less physical activity, but also more energy consumption than needed for a given activity and subsequent increase in body weight. Exercise is often associated with a healthier lifestyle, including a more equilibrated diet, less smoking or alcohol, no overweight, which are modulating factors difficult to dissociate from each other. This situation can be compared to the problems in the risk assessment of coronary heart disease. A study comparing 2073 colon cancer cases to 2466 matched controls that lack of lifetime vigorous leisure-time activity was associated with increased risk of colon cancer, but also high levels of calory intake and a large body mass index (37). These findings suggest that energy balance as a whole seems to be associated with risk of colon cancer. These three factors may operate at different levels in the aetiology of colon cancer, but it seems to be more plausible that they act at the metabolic level rather than locally on colonic epithelium. It has been suggested that it might operate through influences upon serum trigycerides and insulin resistance commonly associated with coronary heart disease and diabetes mellitus (38). Other potential mechanisms of action of exercise involve acceleration of intestinal transit time, with subsequent reduction of contact time between the colon mucosa and carcinogens present in the bowel lumen. An increased colonic blood flow might result in a faster "wash-out" of carcinogens. A decreased ratio of secondary to primary bile acids, or an elevated production of some prostaglandins have also been suggested.

Estrogens

During the past 20 years, mortality from colorectal cancer has decreased slightly in men, but much more in women. A possible explanation for this difference is the increasing use of postmenopausal hormone-replacement therapy. (39). Estrogens may exert a protective effect through different mechanisms, including a decreased production of secondary bile acids, a decreased production of insulin-like growth factor I, or by direct actions on the colorectal epithelium. The "Nurses' Health Study" shows a protective effect of postmenopausal use of hormones, but limited to those currently receiving therapy, and disappearing 5 years after cessation. This effect is limited to the risk of developing large adenomas of more than 1 cm in diameter, which suggest that estrogens probably act at late stages of colorectal carcinogenesis (9).

Vitamins and antioxidants

Some vitamins with antioxidants properties, such as beta carotene, alpha-tocopherol or retinoids, have been proposed as protective agents, because of their presence in high concentration in fruits and vegetables. However, at least until now, no prospective study does support that hypothesis. One prospective placebo-controlled randomised study does not show any difference in the rate of adenoma formation at colonoscopy after one and four years of receiving beta-carotene, vitamins C and E, either alone or combined (40).

Nonsteroidal anti-inflammatory drugs

More recently, the potential role of nonsteroidal anti-inflammatory drugs (NSAIDs) in chemoprevention has raised a lot of promises. Since 1897, when the formulation of acetylsalicylic acid was first recognised, it has become the most widely utilised molecule in the treatment of fever, inflammation or pain. Its field of application has been considerably enlarged when its beneficial use in cardio-vacular diseases has been proven. The gastroenterologists usually consider NSAIDs as an aggressor, because they are mostly confronted to their toxicity, gastro-duodenal ulcer and bleeding. This situation might be due to change in a near future, if their protective action against colorectal cancer is established for sure.

The first observation goes back to 1980, when indomethacin was shown to reduce the size of desmoïd tumours in patients with Gardner's syndrome (41). Other investigators reported that was effective in reversibly decreasing the number of polyps in familial adenomatous polyposis (42). These findings were further confirmed by randomised placebo-controlled studies, which demonstrated that sulindac reduced the size of rectal adenomas of patients with FAP and ileo-rectal anastomosis, with a complete response rate up to 76% (43). The enthusiasm towards these compounds has been consistently growing, since the first epidemiological case-control studies have been published, that demonstrate the beneficial effects of aspirin and other NSAIDs (piroxicam, sulindac, indomethacine,...) in the reduction of colorectal cancer incidence and mortality rates, up to 40 to 50% in individuals taking them on a regular basis (44). In the vast cohort of the Nurses Health Study, in which 550.000 women were followed for the risk of cardiovascular diseases and breast cancer, it appears that the risk for colorectal cancer is best reduced after a regular aspirin use of 10 years, 4 to 6 tablets per week (45). Of course, no final conclusion can be drawn from these epidemiological studies, which might carry some bias, even if other parameters like diet, exercise or body mass index were controlled. Some other factors may have influenced these results, like reasons for taking aspirin, other attributes of a healthier lifestyle, or earlier diagnosis of benign adenomas due to bleeding from platelet aggregation inhibition, or better compliance to screening.

Several experimental studies have been carried out on animal models. Sulindac at different dosages significantly reduces both the number and the size of tumours in the treated rats compared with controls (46). Aspirin causes a significant reduction in 1-2 dimethylhydrazine induced colonic aberrant crypt foci in rats (47). Both piroxicam and sulindac inhibit tumour formation in the APC-min rats model (5).

Their exact mechanism of action is still controversial. NSAIDs may suppress carcinogenesis by numerous potentially antagonist pathways. They inhibit cyclooxygenase (COX)-mediated carcinogen activation. COX catalyses the arachidonate metabolites (prostaglandins), which modulate cell growth and cell transformation. This enzymatic complex may be involved in carcinogenesis by several pathways, including direct activation of carcinogens, production of mutagens, such as malondialdehyde, formation of peroxyl radicals or activation of procarcinogens. In normal cells, the tissue mass is in constant equilibrium, because of a tight regulation of cell proliferation and apoptosis. In neoplasia, this balance between these two processes is deregulated, leading to either increased cell renewal, or decreased cell loss, or both. Sulindac inhibit proliferation of HT-29 cells in culture, which are clonal human colon cancer cells, thus inducing a more quiescent cell cycle (48). Several NSAIDs stimulate apoptosis in HT-29 cells, and reverse the anti-apoptotic effect of prostaglandin E2 in vitro (49). It is still not established whether these two effects require inhibition of prostaglandins synthesis or not. Sulindac sulfone, a major metabolite of sulindac which does not inhibit COX activity, induces apoptosis in cultured colon cancer cells (50). This demonstrate that at least part of NSAIDs' action on cell cycle is not COX -mediated. It is not known which action COX-dependant or independent, is predominant in vivo, but it is likely that both play a role. Last but not least, they exert their protective effect through immune surveillance. NSAIDs may restore the ability of the immune system to eliminate transformed cells, by increasing the presentation of certain antigens which are critical in the immunological recognition of these transformations (51).

The use of NSAIDs in chemopevention is limited by GI toxicity, mostly gastro-duodenal bleeding. It makes no sense to decrease death rates from colorectal cancer on one hand, and to lose patients from digestive haemorrhage on the other one. There are two COX isoforms : COX-1 is expressed constitutively and helps maintain gastric mucosal integrity, acting like a "house keeper" involved in tissue homeostasis. GI toxicity of NSAIDs is related to COX-1 inhibition. COX-2 is not constitutively expressed in normal digestive mucosas. It is induced by cytokines, growth factors and tumour promoters. Its expression is up-regulated in colonic adenomas and carcinomas, in both human specimens and animal models. An elevated COX-2 expression makes colon cancer cells resistant to apoptosis. Specific COX-2 inhibitors are proposed or still in development. They reduce NSAIDs' toxicity, without losing their anti-inflammatory abilities. That might restore the ability of the cells to undergo apoptosis. It is of noticeable importance that 15% of cancer cells and 60% of adenomatous cells do not express COX-2 activity (52). Thus, the best protective agent would be the one with both COX-2 mediated and COX-2 non mediated activities. There are an increasing number of experimental data suggesting that COX-2 selective NSAIDs may exert their protection through the sum of these actions, on the APC-min model (53). A recent placebo-controlled randomised study has shown that celecoxib, a selective COX-2 inhibitor, leaded to a significant reduction in the number of polyps in patients with familial adenomatous polyposis. (54)

NSAIDs represent a most exciting hope in the field of colorectal cancer prevention. Even if it is still too early to draw final conclusions and make population based recommendations, we may expect that upcoming results of well-designed prospective clinical trials will help to answer the many unresolved questions. We still need to determine the optimal dose or schedule of therapy. If indicated, what will be the best age to initiate their regular use ? Should we recommend their use in the entire general population, or restrict it to high risk groups, such as subjects with familial predisposition, having at least one first degree relative suffering the disease ? We still do not know which one is the best molecule. It should be cheap, safe and efficient. Aspirin seems to be a good candidate because of its low cost and wide availability, but its toxicity has to remain acceptable. We do not know whether the rather safe dosages used in cardiovascular diseases prevention will meat their goal in colorectal cancer prevention. COX-2 inhibitors might be the most promising compounds. Their exact place in the present time is still controversial. Cost-effectiveness is of major concern in that field.

It should be noticed that even if NSAIDs exert a proven benefit in reduction of adenomas in FAP, it is reversible, and we do not know their role at the adenoma to cancer stage of the sequence. They will not replace the indication of total coloproctectomy in these patients. Perhaps will they delay surgery in the youngest patients. They might serve as an adjunct to current management by suppressing polyp formation in patients with residual rectum after colectomy. Some recent epidemiological studies have even shown a decrease of other digestive tumours, oesophageal squamous cell carcinoma and adenocarcinoma, and non cardial gastric adenocarcinoma among aspirin regular users (55). Considering all of this, the future of NSAIDs in colorectal cancer prevention looks quite promising.

Interactions between genetic and environmental factors

In 1990, Fearon and Vogelstein proposed their model of a genetic cascade of chromosome alterations, which

operate at successive levels in the polyp-cancer sequence, from hyperproliferative epithelium to early, intermediate, late adenomas, leading to cancer (56). Since then, more mutations have been identified, or their role better understood. This include mutations related to hereditary cancer syndromes, such as the APC gene mutations and mutations leading to defective DNA mismatch repair producing microsatellite instability, as described in hereditary non polyposis colorectal cancer or Lynch syndromes (57). Practical applications have mostly leaded to substantial progress in genetic counselling. One can expect that further development in that field will help selecting individuals susceptible to draw maximal benefit from secondary prevention and colorectal cancer screening. But this genetic cascade of events affect only the genotype, and genetic effects need environmental factors to cause or promote their expression (58). Quoting Michael Hill, *the phenotype is determined by a combination of the genotype and the environment.* Further research may include those environmental factors into the genetic cascade, and perhaps provide explanations or better understanding of the discrepancies observed in epidemiological or experimental dietary or chemoprevention studies.

Conclusions

Prospective intervention studies on colorectal cancer incidence as an endpoint are required to evaluate the actual benefit of dietary intervention or chemoprevention. But these studies will take decades to obtain final conclusions.

When there is enough evidence from studies on biomarkers or animal models that an agent may influence the risk of cancer, it may be tested at the population level, in intervention studies. The US National Cancer Institute is now granting several phase III studies. Dietary recommendations are an important part of the European Community project "Europe Against Cancer", which aims at decreasing the progression rate of cancer by 15%. These health advises include a reduction in animal fat consumption and an increase in fiber intake, which are now accepted as standard recommendations by most scientists.

Primary prevention of colorectal cancer brings a lot of hope, even if we still lack final evidence in many, if not most fields. As a matter of fact, dietary recommendations and chemoprevention may be considered as part of a healthier lifestyle, with potential protective effect not only on the risk of colorectal cancer, but also on other cancers such as breast cancer, or coronary heart diseases, as proposed for low fat diet, physical activity or NSAIDS. In that matter, some important points should not be underscored. Compliance is a key factor in predicting the optimal benefit of chemoprevention. A single daily all-inclusive miracle-tablet might be more acceptable than drastic permanent dietary modifications. It can take several generations before such changes can be achieved. Considering this, the most encouraging approach might be chemoprevention with selective COX-2 inhibitors, if their beneficial effect is confirmed. Even if the benefit is objective, it does not decrease the need for screening and secondary prevention, because the risk is not totally eliminated. Thus, there is no potential benefit in terms of cost at that level. Those pending questions must not decrease the enthusiasm for the future developments in the field of primary prevention of colorectal cancer.

Physicians involved in colon cancer therapy must be aware of the need to put together all levels of fight, including treatment, secondary prevention, and primary prevention, to have a chance to reduce significantly the impact of this devastating disease on public health and quality of life.

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