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Point: From animal models to prevention of colon cancer. Systematic review of chemoprevention in min mice and choice of the model system

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Abstract

The Min (Apc(+/-)) mouse model and the azoxymethane (AOM)-rat model are the main animal models used to study the effect of dietary agents on colorectal cancer. We recently reviewed the potency of chemopreventive agents in the AOM-rat model (Corpet and Taché, 2002). Here we add the results of a systematic review of the effect of diet and agents on the tumor yield in Min mice, based on the results of 179 studies, from 71 articles, and displayed also at the website <http://www.inra.fr/reseau-nacre/sci-memb/corpet/indexan.html>. The efficacy of agents in the Min mouse model and the AOM-rat model correlated ($r=0.66$, $p<0.001$), although some agents that afford strong inhibition in the AOM-rat and the Min mouse increase the tumor yield in the large bowel of mutant mice for reasons not yet understood. Thus, piroxicam, sulindac, celecoxib, difluoromethylornithine, and polyethylene glycol could promote carcinogenesis in the colon of mice. We also compare the results of rodent studies with those from clinical intervention studies of polyp recurrence. We found that the effect of most of the agents tested is consistent across the animal models, except the above-mentioned puzzling mouse colon. Thus our point is that the rodent models can provide guidance in the selection of prevention approaches to colon cancer, in particular suggesting the likely importance of polyethylene glycol, hesperidin, protease inhibitor, sphingomyelin, physical exercise, epidermal growth factor receptor kinase inhibitor, (+)-catechin, resveratrol, fish oil, curcumin, caffeate and thiosulfonate as preventive agents.

MESH Keywords Animals ; Anticarcinogenic Agents ; therapeutic use ; Azoxymethane ; diagnostic use ; Chemoprevention ; Colonic Neoplasms ; chemically induced ; prevention & control ; Diet ; Disease Models, Animal ; Humans ; Mice ; Mice, Mutant Strains ; Precancerous Conditions ; chemically induced ; prevention & control ; Randomized Controlled Trials as Topic ; Rats

Author Keywords animal-model ; diet ; chemoprevention ; colon-carcinogenesis ; Min-mice ; chemically-induced

Introduction

Puzzling results were presented at recent meetings of the American Association for Cancer Research. The feeding of the nonsteroidal anti-inflammatory drugs (NSAIDs) piroxicam or sulindac to mutant mice with spontaneous tumors, strikingly increases the tumor yield in their colon (1–3). However, NSAIDs are widely accepted chemopreventive agents against colon cancer in humans (4). These results raise questions about either the animal model, or the NSAIDs protection. We have thus reviewed the results of dietary chemoprevention studies in animal models of colorectal cancer and compared them with the results of clinical intervention studies, looking for consistency among the models.

Two animal models for preclinical testing of chemopreventive agents

Since 1970 investigators have searched for diets or agents that suppress colorectal tumors in rodents. Rodents have almost no spontaneous colon cancer, and a carcinogen is needed to induce the tumors. Most chemopreventive agents were thus tested in rats, usually male Fisher 344, given AOM injections. AOM is a specific colon carcinogen, like its precursor, dimethylhydrazine. The tumors induced are often mutated on K-ras and beta-catenin genes (5), but seldom (15%) on the adenomatous polyposis coli (Apc) gene, and never on the p53 gene (6). Other rodents (mice), and other colon carcinogens were used less frequently, e.g., specific nitrosamines, and heterocyclic amines like 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP). PhIP induces the Apc mutation frequently (40–60%) (7) and microsatellite instability (8), but no K-ras or p53 mutations (9–10). AOM is not present in our daily diet, but PhIP is. However, PhIP is almost never used because AOM is less expensive, more potent, and more convenient to use than PhIP. Chemopreventive treatment can be begun before exposure to the carcinogen and during the initiation phase, during the promotion-progression phase, or through both phases. The incidence of colon tumors is the major endpoint in most rats studies. Carcinogen-induced tumors produced in the rat colon share many characteristics with human colorectal cancer, except that they have a lower tendency to metastasize.

In 1990, the mutant Min mouse was found with multiple intestinal neoplasia (11). It was shown to have a mutated Apc gene, similar to that in patients with familial adenomatous polyposis, and in many sporadic cancers. This promising animal model mimics the rapid development of adenomatous polyps that affect humans with germline inactivation of one Apc gene. But the K-ras mutations observed in many human tumors were not detected in Min mice polyps (12), and p53 inactivation, frequent in human cancers, does not raise tumor number in Min mice (13). Following the Min mouse discovery with truncated Apc in position 850, other mice have been genetically modified so that one or more oncogenes hold a germline mutation (e.g., truncated Apc in positions 716, 1309, or 1638, and mutated Msh2

or Mlh1). A mutation on Msh2 or Mlh1 genes leads to mismatch repair defect, which makes these mice a model for human hereditary nonpolyposis colorectal cancers (14). These mutant mouse models have increased our understanding of carcinogenesis. They have also provided a model to evaluate the effect of diets and chemopreventive agents. Compared with the AOM-rat model, the use of mutated mice avoids the hazard of carcinogen handling, and leads to shorter studies. Dietary treatments are initiated in mice by the age of 4–5 weeks, when tumors may be already present (except for a few in utero studies). This timing mimics human clinical trials, where dietary treatments are given to adults, likely to bear minute polyps, the visible ones having been removed before randomization. The number of tumors in the small intestine is the primary endpoint in most mouse studies. The major drawback of these mutant models is that, in contrast with the human situation, the mouse tumors occur predominantly in the small intestine and not in the colon.

There are now sufficient results reported from the AOM-rat and Min mouse colon cancer prevention models to make it possible to compare the results of different approaches and to begin to assess which provides the best prediction of response in clinical intervention studies. We consider first the previous review of results of interventions with the rat model, then review results obtained with the Min model.

Review on dietary chemoprevention in the AOM-rat and Min mouse models

Data from our previous systematic review on chemoprevention in the rat model (15) were gathered from 146 articles with the tumor endpoint, and 137 articles with the aberrant crypt focus endpoint, a putative preneoplastic lesion. Tables were built with potency of each agent or diet to reduce the tumor incidence or the number of aberrant crypt foci in the colon of rats. Both tables are available on a website with sorting abilities, <http://www.inra.fr/reseau-nacre/sci-memb/corpet>. Agents of outstanding potency, that fully suppress colon adenocarcinoma and/or consistently inhibits adenoma and aberrant crypt foci in several independent AOM-rats studies, were (ranked list): polyethylene glycol (PEG), celecoxib, hesperidin, difluoromethylornithine (DFMO) and piroxicam (combined or not), sulindac (sulfone or sulfide), and ursodeoxycholic acid. In addition, treadmill exercise, and S-methyl-methane-thiosulfonate suppressed carcinoma (supported by a single study each). Last, Bowman-Birk protease inhibitor and sphingomyelin were consistently efficient in AOM-initiated mice (15).

All publications relating to the effect of dietary agents tested in Min mice, and other mice with mutations resulting in intestinal tumors, were identified from three databases, ISI Current Contents, Medline, and the American Association for Cancer Research website, for the period from 1990 to May 2002. Data were gathered from 63 articles and eight meeting abstracts, yielding 179 comparisons between a control and a treated group of mice. A primary table (not shown) was built including the following data: mouse strain, mutation, treatment dose duration and vehicle, the number of intestinal adenomas in treated and control groups, the significance of the treatment effect, and, when reported, the size of intestinal adenomas, and the specific number of colonic adenomas. Some papers did not report small and large bowel data separately. In those cases, we reported the total number of adenomas instead of small intestinal adenomas. This primary table was abstracted to give the efficacy of each treatment to reduce the number of adenomas in the small intestine, and in the colon, of mutated mice (Table 1). The results are reported as a percentage of control values. The table is available on a website with sorting abilities, allowing to rank agents by potency, <http://www.inra.fr/reseau-nacre/sci-memb/corpet/indexan.html>.

The table clearly shows that NSAIDs are, by far, the most potent agents to suppress tumor formation in the small intestine of Min mice. Notably, piroxicam and sulindac decreased the tumor yield by 90% or more in several independent studies. As shown on Table 1 (ranked by potency, on the website), piroxicam or sulindac were used in all of the top-25 studies but one, which involved the epidermal growth factor receptor kinase inhibitor, EKB-569. Specific anti-cyclooxygenase (COX)-2, like celecoxib or MF-tricyclic, were not more potent than non selective NSAIDs. Other agents were less potent than NSAIDs and the best ones decreased the tumor yield by 60–70%: (+)-catechin, resveratrol, fish oil (two studies), curcumin, folic acid and caffeic acid phenethyl ester. Following agents were clearly less potent: cellulose, copper, DFMO, PEG, wheat bran, sphingomyelin, uroguanylin and selenium compound p-XSC.

Comparison of results obtained with the two prevention models

Fig. 1 shows that many agents that suppress tumors in the Min mouse intestine (Table 1) also decrease the incidence of colorectal cancer in AOM-initiated rats (15). A significant correlation was found between the efficacy of agents tested in both models ($r=0.66$, $N=36$, $p<0.001$). It is clear that the most potent chemopreventive agents in the Min mouse small intestine, are also potent in the colon of AOM-initiated rats, and the animal models thus seem consistent.

Min mice have many tumors in the small intestine (median number 34), but few tumors in the colon (median, 1.0) (Table 1). In contrast, human tumors are rarely found the small intestine, but frequently in the colon. This discrepancy between the mouse model and the human situation led us to examine the effect of diets on the tumor yield in the **colon** of mutated mice. We thus calculated the ratio between treatment effect in the small intestine and in the colon (two last columns in Table 1). The table was sorted by this ratio, showing that the median ratio was 0.95: on average, the agents have similar efficacy on large and small intestinal tumors. The top and bottom of this ranked table are shown on Table 2, displaying agents with a ratio below 0.4 or above 2.5. Several studies with NSAIDs and peroxisome proliferator-activated receptor (PPAR) agonists show much weaker protection (or specific promotion) to the colon than to the small intestine. In addition high fiber diets, PEG and *Citrobacter rodentium* can increase specifically the tumor yield in the colon. In

contrast resveratrol, folic acid, uroguanylin, selenium in broccoli, and fructo-oligosaccharides afforded a specific protection to the colon (Table 2).

Some discrepancies between the small and large bowel are easy to explain, particularly when the effect is modulated by the gut flora. For instance, fructo-oligosaccharides are not digested in the small intestine, but fermented by the microflora in the colon, where they yield butyrate, a possible apoptosis inducer. It may explain why fructo-oligosaccharides can decrease the tumor yield in the colon of Min mice, but not in their small intestine (25). In contrast, the promotion of tumors by *Citrobacter rodentium* is limited to the colon, where the bacterial density is much higher than in the small intestine (58). The colorectal position of cancers in people is believed to follow, at least in part, the presence of an abundant colonic microflora. From this point of view, the small intestine of Min mice may not be a proper model of the human colon. Also, the tumor promotion by PPAR gamma agonists is much stronger in the colon than in the small intestine. This pattern reflects PPAR gamma expression, high in the colon, low in the rest of the gut, in both mice and humans (83).

In contrast, it is surprising that the most potent chemopreventive agents in the Min mouse small intestine, also potent in the colon of AOM-initiated rats, could sometimes increase the tumor yield in the colon or in the ileum of mutated mice. The NSAIDs piroxicam, sulindac, and celecoxib strongly decrease the number of tumors in the small intestine of mutant mice (Table 1), and strongly decrease the tumor incidence in AOM-initiated rats (84, 85, 86). In contrast, piroxicam increased the number of tumors in the colon of Min mice in four studies out of six (Table 1). In addition, piroxicam caused a ten-fold dose-dependant increase in tumor multiplicity in the distal intestine of *Msh2*^{-/-} mice (1). In two studies out of three, the sulindac protection in the colon of Min mice is much weaker than in the small intestine (Table 2). In three studies out of four, no protection is seen in the colon of mice with *Msh2* or *Apc716* mutations (Table 1). In addition, sulindac treatment significantly increased colonic tumors in four mutated mouse models: *Apc* Min, *Apc1638*, *Apc1638/Mlh1*, and *Mlh1* mice (2, 3). For instance, in *Mlh1*^{+/-} mice, sulindac treatment increased the colon tumor incidence from 20% to 91% (3). Also, a late treatment with a high dose of celecoxib increased the tumor yield in the colon of Min mice (45). Thus, very potent chemopreventive NSAIDs could promote tumors in the colon of mutated mice.

Other agents than NSAIDs also yield discrepant results in the colon of rats and mice, for instance DFMO, PEG and inulin. DFMO blocks ornithine decarboxylase, it strongly decreases colon tumor incidence in rats (87), and suppresses polyps in the small intestine of Min mice, but it increased the number of large polyps in the colon of Min mice (38). PEG, a mild laxative, is a strikingly potent chemopreventive agent in rats (88, 89), but in one study out of two (65, 66), it strikingly increased the tumor yield in the colon of Min mice (Table 1). Last, inulin, a natural non digestible oligosaccharide, decreases carcinogenesis in rats, but increases the tumor yield in the colons of Min mice (22, 27).

The reason for these puzzling discrepancies is unclear. Some differences seem spurious: due to the very low number of tumors in the colon of Min mice, an increase may be seen when there is no true effect. However, the promotion by sulindac or piroxicam is seen in several independent studies. Indeed, in Min mice, differences in key enzymes make small and large bowel mucosas react differently to COX inhibitors. Phospholipases A-2 (PLA-2) are key enzymes at the start of the arachidonic acid cascade, that lead to the promoting prostaglandin E2. Arachidonic acid is released from phospholipids by either the secretory sPLA-2 or the cytosolic cPLA-2 (90). cPLA-2 is upregulated in tumors from the colon of humans and rats, and from the mouse small intestine (91, 92). This difference is not seen in the colon of Min mice, where cPLA-2 mRNA is high in both normal and tumor tissues (93). Moreover, mice with a mutated cPLA-2 gene have smaller tumors in the small intestine than wild controls, but the effect is not seen in the colon. In contrast, sPLA-2 does not seem essential for carcinogenesis in humans (94, 95), in PhIP-initiated rats (96), or in Min mice. Indeed, C57Bl6/Min mice with a mutated sPLA-2 gene have more tumors than AKR/Min mice with the intact sPLA-2 gene (97). COX-2 converts arachidonic acid to prostaglandin. It is over-expressed in tumors from the colon of humans and rats, and from the mouse small intestine (92). In *Apc*-mutated mice, the knocking out of COX-2 dramatically reduces the number and size of small intestinal polyps (54). Conversely, COX-2 upregulation is associated with the development of polyps in the small intestine. In contrast, COX-2 protein is not over-expressed in colonic polyps. COX-2 expression is higher in the large than in the small bowel mucosa (98). Thus, prostaglandin producing enzymes are more expressed, but mice have fewer tumors, in the colon than in the small intestine. This may explain that, in several mice studies, NSAIDs do not prevent, but promote, colon tumors. Curiously, the contrasts observed between tumors and normal mucosa in the colon of humans and rats, are better reproduced in the small than in the large bowel of Min mice.

Polyamines levels are lower in the colon than in the small intestine of Min mice. In spite of a high ornithine decarboxylase expression, a colonic antizyme decreases the polyamine pool (38). This low level of polyamines in the colon may explain why Min mice have few polyps in the colon. Moreover, DFMO treatment reduces polyamine levels in human colon, but not in the colon of Min mice. This may explain why DFMO does not suppress colonic polyps in Min mice. Again, this would suggest that the colon of rats and the small intestine of Min mice are better models than the Min mouse colon.

Comparison of humans data with animal models data

Finally, we would like to know how the results with the two models compare with those obtained to date in clinical trials directed at preventing the recurrence of colonic polyps. How well do the animal models predict what happens in humans? To answer this question we built a table showing the effect of dietary interventions on tumors in rats and mice, and on the recurrence of colonic polyps in humans (Table 3). The mean effect in rats was extracted from a published data base of positive studies (15), to which were added null and negative studies. The mean effect in Min mice was calculated from Table 1. Table 3 is obviously a first approach to such a comparison, since no account was taken of the dose used, and the data presented are not homogeneous across different models.

Table 3, none-the-less, shows that the effect of most of the diets or agents is consistent across the various models though discrepancies are seen between the effect of agents in humans and in animals as follows.

- - NSAIDs strongly decrease the tumor yield in the colon of AOM-injected rats, and in the small intestine of mutant mice. This is consistent with epidemiological studies suggesting that, taken collectively, NSAIDs might decrease the colorectal cancer incidence by 45% in humans (4, 116). It is also consistent with the effect of celecoxib and sulindac which decrease the polyp number in familial adenomatous polyposis patients trials. However, as detailed above, several independent studies (but not all) show that some NSAIDs can increase the tumor yield in the colon of mutant mice.

- - Wheat bran consistently reduces carcinogenesis in animals, but has apparently no significant effect in humans, a discrepancy for insoluble fibers, already pointed out by Giovannucci (117). A soluble fiber, psyllium, decreases carcinogenesis in rats, but increases the tumor recurrence in human volunteers. However, both results are only supported by a single study each. In addition, other soluble fibers similar to psyllium often show promoting properties in AOM-induced rats, an effect that fits the human trial result.

- - Rats and mice fed a high fat diet have usually more tumors than controls fed a low fat diet. In rodents, the relationship between the colon cancer incidence and the intake of fat remains true when controlled for calorie consumption. Fatty diets with high linoleic acid content, and n-6-polyunsaturated fatty acids, seem particularly consistent promoters in rodents (105). In contrast, neither human trials nor observation studies support fat, or linoleic acid, as tumor promoters in humans (118), a discrepancy already pointed out by Giovannucci (117).

- - Caloric reduction is a strategy that seems very efficient in animals (Table 3). Overnutrition could be seen as the most potent “carcinogen” in rodents (119). According to Willett, a positive energy balance (caloric intake versus physical activity) is the most powerful and consistent dietary influence on carcinogenesis (120). No published human trial specifically tested the effect of caloric reduction. However, a side effect of interventions with low-fat diet, and with fruits and vegetables, was a modest reduction in caloric intake (106–108). The lack of reduction in polyp recurrence seen in these trials (Table 3) suggests the caloric reduction was too small to reduce insulin resistance, a supposed link between overnutrition and carcinogenesis (117, 121).

- - That fruits and/or vegetables consumption protects against colorectal cancer is a dogma supported by many epidemiological studies (122–123), an association that may have been overstated (124). This dogma is challenged by all the experimental studies in rats, mice and humans (Table 3). Indeed, a mixture of fruits and vegetables reproducing the people typical intake marginally increased the tumor yield in most animal studies (71, 109–111), but large amounts of black raspberries or of orange juice can inhibit carcinogenesis in rats (125).

Conclusions

There is a close agreement between the many results obtained in the colon of AOM-initiated rats and in the small intestine of Min mice (Fig. 1). There is a reasonable association between these animal studies and the more limited clinical studies (Table 3). However, some results obtained in the colon of Min mice are discrepant from those of the Min mouse small intestine and the AOM-rats, which suggests they should be disregarded until they can be explained. Many promising agents strongly and consistently suppress tumor formation or growth in the small intestine of Min mice, or in the colon of AOM-injected rats. Some of them have already been tested in completed clinical trials: selenium, celecoxib, aspirin, sulindac, calcium, wheat bran, low fat diet, fruits and vegetables diet, beta-carotene, vitamin C and E (Table 3). Others are presently under study in humans: ursodeoxycholate, piroxicam, DFMO, and folic acid. Most published trials show no reduction in polyp recurrence, and the significant protection afforded by celecoxib, aspirin or calcium was modest (Table 3). We thus need new agents or strategies to reduce cancer load.

A conservative approach would be to include an agent or a diet in a human clinical trial only when it shows preventive properties in all available models. We think that this approach might be too conservative, and would have disqualified the testing of celecoxib, piroxicam, sulindac, DFMO, calcium and folic acid in humans, since they have shown promoting properties in some preclinical studies. Our point is that it is appropriate to proceed now with the agents that are particularly potent against carcinogenesis in either rats or mice. The data we have summarized and compared would suggest that these include: PEG, hesperidin, Bowman-Birk protease inhibitor, sphingomyelin, physical exercise, and S-methyl-methane-thiosulfonate (from the AOM-rat model), and EKB-569, (+)-catechin, resveratrol, fish oil, curcumin, and caffeic acid phenethyl ester (from the Min mouse model). These agents showed no toxicity in rodents, and some of them are

already used daily by humans on a large scale (PEG, exercise, catechin, fish oil, curcumin). The safety of others, notably EKB-569, still need to be evaluated (126).

Since human studies are extremely long and costly, they require stringent preliminary studies to evaluate side-effects and optimal dosage. In addition, the long term administration of an agent to many people poses ethical problems, as beta-carotene trials in smokers sadly showed. The use of surrogate endpoint biomarkers in step-wise clinical trials might help to decrease both cost and risk. For instance, a short trial on the suppression of aberrant crypt foci in the colon of volunteers (127) could be done before a standard trial on adenoma recurrence. This approach would be particularly appropriate for agents like PEG that clear the aberrant crypt foci quickly from the mucosa (89). This strategy could eventually provide evidence for safe dietary interventions for the prevention of colorectal cancer.

The abbreviations used are

NSAID: nonsteroidal anti-inflammatory drug

AOM: azoxymethane

Apc : adenomatous polyposis coli

PhIP: 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

PEG: polyethylene glycol

DFMO: difluoro-methylornithine

COX: cyclooxygenase

PPAR: peroxisome proliferator-activated receptor

PLA-2: phospholipase A-2

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Figure 1

Correlation between the effect of various agents on the number of adenomas in Min mice small intestine and on the incidence of colon tumors in AOM-initiated rats. The correlation coefficient was 0.66 with all the points ($p < 0.001$), and 0.82 after exclusion of two outliers (methionine and folic acid).

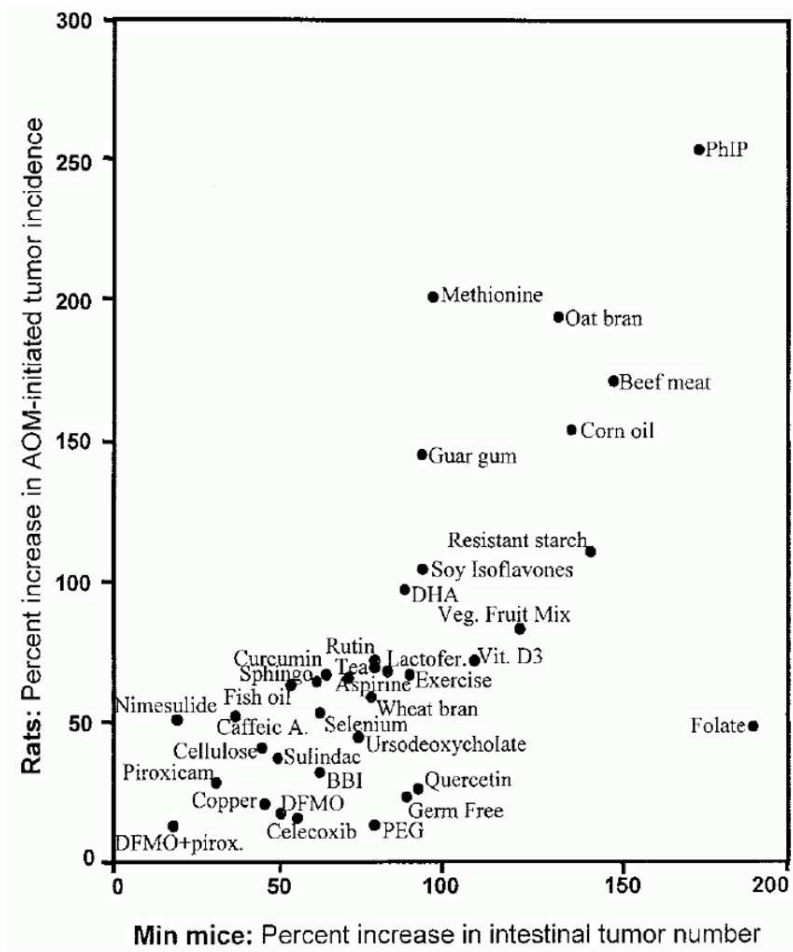


Table 1

Effect of dietary agents on the tumor number in the small intestine and in the colon of Min mice, and other mutant mice.

| Category | Treatment/mutation ^a | Dose ^b | Duration ^c | N ^d | Adenoma number ^e | | Treatment effect: treated % control | | Ref. |
|-----------|---------------------------------|--------------------------|-----------------------|----------------|-----------------------------|-------|-------------------------------------|------------|------|
| | | | | | small int. | colon | small int. | colon | |
| Bile acid | Chenodeoxycholic | 0.50% | 10 w | 1 | 33 | 0.4 | 77 | 150 | 16 |
| Bile acid | Ursodeoxyc. +sulindac | 1500–4500 +75 ppm | | 2 | 18 | | 15 | | 17 |
| Bile acid | Ursodeoxyc. +sulindac | 500 +75 ppm | | 1 | 18 | | 30 | | 17 |
| Bile acid | Ursodeoxycholic. | 500–1500 ppm | | 2 | 18 | | 73 | | 17 |
| Fat | Arachidonic acid | 1% | 7 w | 1 | 54 | | | 101 | 18 |
| Fat | Corn Oil | 10% vs 3% | 150–300 d | 2 | 23 | 1.8 | 137 | 212 | 19 |
| Fat | DHA/Apc716 | 3% female | 7 w | 1 | 219 | | 31 | | 20 |
| Fat | DHA/Apc716 | 3% male | 7 w | 1 | 193 | | | 144 | 20 |
| Fat | Fish oil K85 | 0.4% male | 17w/w1 | 1 | 108 | 1.0 | 33 | 160 | 21 |
| Fat | Fish oil K85 | 1.25–2.5% male | 17w/w1 | 2 | 108 | 1.0 | 74 | 65 | 21 |
| Fat | Fish oil K85 | 0.4-1.25-2.5% female | 17w/w1 | 3 | 73 | 0.8 | 55 | 38 | 21 |
| Fat | HighFat LowFiber | fat:cellul. 22:0 vs 7:5% | 5–6 w | 1 | 35 | 1.8 | 98 | 78 | 22 |
| Fat | Low soybean oil | 5% vs 20, no fiber diet | 60 d | 1 | 30 | 0.4 | 62 | 57 | 23 |
| Fat | Western diet/Apc1638 | Fat+, Ca-, vit.D- | 14–34 w | 2 | | 1.0 | | 233 | 24 |
| Fiber | Cellulose | 5–10% vs 0, in 20%fat | 60 d | 2 | 30 | 0.4 | 45 | 107 | 23 |
| Fiber | Fructo-oligosaccharide | 5.8% | 42 d | 1 | 50 | 2.1 | 93 | 33 | 25 |
| Fiber | Fructo-oligosaccharide | 5.8% in T-cell depleted | 42 d | 1 | | 0.4 | | 200 | 26 |
| Fiber | Guar gum | 5–10% vs 0, in 20%fat | 60 d | 2 | 30 | 0.4 | 59 | 93 | 23 |
| Fiber | High fiber rodent chow | fiber:fat 18:6 vs 0:20% | 60 d | 1 | 29 | 0.4 | 96 | 271 | 23 |
| Fiber | Inulin | 2.5% | 5–6 w | 1 | 35 | 1.8 | 140 | 133 | 22 |
| Fiber | Inulin | 10% | 9 w | 1 | 55 | 0.6 | 123 | 211 | 27 |
| Fiber | Oat bran | 10% | 5–6 w | 1 | 35 | 1.8 | 133 | 100 | 22 |
| Fiber | Resistant starch | 18.8% | 42 d | 1 | 50 | 2.1 | 99 | 143 | 25 |
| Fiber | Rye bran | 10% | 5–6 w | 1 | 35 | 1.8 | 75 | 78 | 22 |
| Fiber | rye bran | 10%/inulin diet | 5–6 w | 1 | 40 | | 91 | | 28 |
| Fiber | Wheat bran | 10% | 5–6 w | 1 | 35 | 1.8 | 99 | 117 | 22 |
| Fiber | Wheat bran | 7.1% | 42 d | 1 | 50 | 2.1 | 94 | 71 | 25 |
| Fiber | Wheat bran | 5–10% vs 0, in 20%fat | 60 d | 2 | 30 | 0.4 | 53 | 143 | 23 |

| | | | | | | | | | |
|---------------|-------------------------|------------------------|------------|---|-----|-----|------------|------------|----|
| Fiber | Wheat bran, fat-/Apc716 | bran:fat 20:5 vs 3:20% | 7 w | 1 | 211 | 2.0 | 64 | 36 | 29 |
| HAA | IQ/Apc716 | 300 ppm | 11 w | 1 | 254 | | 84 | | 30 |
| HAA | MeIQx/Apc716 | 400 ppm | 11 w | 1 | 254 | | 87 | | 30 |
| HAA | N-OH-PhiP/Apc716 | 50 mg/kg × 5 inj. | 5 d/d26 | 1 | 17 | | 335 | | 30 |
| HAA | PhiP | 50 mg/kg × 8 inj. | pups 3 w | 1 | 30 | 0.6 | 789 | 519 | 31 |
| HAA | PhiP | 25 mg/kg × 8 inj. | pups 3 w | 1 | 30 | 0.6 | 524 | 145 | 31 |
| HAA | PhiP | 50 mg/kg × 1 inj. | 7–11 w | 2 | 47 | 0.6 | 346 | 297 | 32 |
| HAA | PhiP | 10 mg/kg × 1 inj. | 7–11 w | 2 | 47 | 0.6 | 188 | 157 | 32 |
| HAA | PhiP | 50 mg/kg × 4 inj. | 4 w | 2 | 72 | 0.7 | 108 | 78 | 33 |
| HAA | PhiP/Apc1638 | 0.03% male&fem. | 182 d | 1 | 3 | | 234 | | 34 |
| HAA | PhiP/Apc716 | 400 ppm | 8 w | 1 | 147 | | 114 | | 30 |
| inhib. EGF | EKB-569 | 150 ppm | 60 d | 1 | 20 | | 13 | | 35 |
| inhib. EGF | EKB-569 +sulindac | 150 +37.5 ppm | 60 d | 1 | 20 | | 4 | | 35 |
| inhib. EGF | EKI-785 | 300 ppm | 60 d | 1 | 17 | | 56 | | 35 |
| inhib. EGF | EKI-785 +sulindac | 300 +150 ppm | 60 d | 1 | 17 | | 5 | | 35 |
| inhib. iNOS | Aminoguanidine | 1500 ppm in water | 10 w | 1 | 73 | 0.8 | 69 | 63 | 36 |
| inhib. iNOS | Arginine deficient diet | No arginine diet | 10 w | 1 | 102 | 0.2 | 67 | 300 | 36 |
| inhib. iNOS | PBIT | 100 ppm/high fat diet | 80 d | 1 | | | 66 | 10 | 37 |
| inhib. ODC | DFMO | 2% | 69 d | 1 | 45 | 3.5 | 46 | 92 | 38 |
| inhib. ODC | DFMO | 1% | 61 d | 1 | 42 | | 57 | | 39 |
| inhib. ODC | DFMO +piroxicam | 1% +50 ppm | 61 d | 1 | 42 | | 27 | | 39 |
| inhib. desat. | SC26196 n-6 desaturase | 100 mg/kg/d | 7 w | 1 | 54 | | 63 | | 18 |
| NSAID | 4-ASA or 5-ASA | 500 ppm | 75 d | 2 | 84 | | 122 | | 40 |
| NSAID | 5-ASA balzazide | 250 mg/kg ? | 90 d | 1 | 22 | | 28 | 21 | 41 |
| NSAID | 5-ASA balzazide | 62–125 mg/kg ? | 90 d | 2 | 22 | | 49 | | 41 |
| NSAID | Aspirine | 250–500 ppm | 7 w | 2 | 36 | 1.0 | 48 | 65 | 42 |
| NSAID | Aspirine | 400 ppm | 370 d/d-21 | 1 | 34 | | 74 | | 43 |
| NSAID | Aspirine | 200 ppm | 130 d/d21 | 1 | 34 | | 115 | | 43 |
| NSAID | Piroxicam | 0.5 mg/mouse/d | 7 d | 1 | 49 | | 5 | | 18 |
| NSAID | Piroxicam | 25-50-100 ppm | 61 d | 3 | 42 | | 66 | | 39 |
| NSAID | Piroxicam | 50-100-200 ppm | 6 w | 3 | 17 | 0.6 | 23 | 150 | 44 |
| NSAID | Piroxicam | 50 ppm | 25 d/d55 | 1 | 23 | 0.8 | 35 | 169 | 45 |
| NSAID | Piroxicam | 50 ppm | 50 d/d30 | 1 | 22 | 1.5 | 23 | 40 | 45 |

| | | | | | | | | | |
|---------|-----------------------|-----------------------|----------|---|-----|------|-----------|-------------|-----|
| NSAID | Piroxicam | 200 ppm | 90–180 d | 3 | 53 | | 4 | | 46 |
| NSAID | Piroxicam | 200 ppm | 6–14 d | 3 | 53 | | 7 | | 46 |
| NSAID | Piroxicam | 200 or 220 ppm | 75 d | 2 | 68 | | 18 | | 40 |
| NSAID | Piroxicam | 200 ppm | 2–4 d | 2 | 53 | | | 64 | 46 |
| NSAID | Piroxicam/Apc1309 | 0.05% | 10 w | 1 | 31 | 2.6 | 52 | 56 | 47 |
| NSAID | R-flurbiprofen | 10 mg/kg/d or/2d gav. | 21 d | 2 | 23 | | 35 | | 48 |
| NSAID | Sulindac | 160 ppm | 11.5 w | 1 | 12 | 0.4 | 1 | 25 | 49 |
| NSAID | Sulindac | 320 ppm | 80 d | 1 | 41 | 0.8 | 7 | 33 | 50 |
| NSAID | Sulindac | 0.6 mg/mouse/d | 7 d | 1 | 46 | | 48 | | 18 |
| NSAID | Sulindac | 160 ppm | 10 w | 1 | 17 | 4.5 | 51 | 67 | 51 |
| NSAID | Sulindac | 75–150 ppm | | 2 | 18 | | 22 | | 17 |
| NSAID | Sulindac | 160 ppm | 75 d | 1 | 84 | | 16 | | 40 |
| NSAID | Sulindac | 300ppm | 10 w | 1 | 72 | | | 68 | 52 |
| NSAID | Sulindac | 150 ppm | 60 d | 1 | 17 | | 26 | | 35 |
| NSAID | Sulindac/Apc716 | 150 ppm | 8 w | 1 | 201 | | 62 | 100 | 53 |
| NSAID | Sulindac/Apc716 | 12 mg/kg/d | 8 w | 1 | 424 | 1.8 | 84 | 50 | 54 |
| NSAID | Sulindac/MinMsh2-- | 13mg/kg/d | 4 w | 1 | 354 | 13.0 | 83 | 108 | 55 |
| NSAID | Sulindac/MinMsh2± | 13mg/kg/d | 22 w | 1 | 44 | 4.8 | 74 | 104 | 55 |
| NSAID | Sulindac sulfone | 50 mg/kg/d gav. | 42 d | 1 | 25 | | | 77 | 48 |
| NSAID/2 | Celecoxib | 1500 ppm | 25 d/d55 | 1 | 23 | 0.8 | 48 | 253 | 45 |
| NSAID/2 | Celecoxib | 500–1500 ppm | 50 d/d30 | 2 | 22 | 1.5 | 29 | 37 | 45 |
| NSAID/2 | Celecoxib | 150–500 ppm | 25–50 d | 3 | 23 | 1.1 | 73 | 65 | 45 |
| NSAID/2 | JTE-523 | 100 ppm | 8 w | 1 | 123 | | 68 | | 56 |
| NSAID/2 | MF-tricyclic/Apc716 | 3.5–14 mg/kg/d | 8 w | 2 | 424 | 1.8 | 44 | 19 | 54 |
| NSAID/2 | MF-tricyclic/MinMsh2± | 13 mg/kg/d | 4–22 w | 2 | 200 | 9.0 | 46 | 63 | 55 |
| NSAID/2 | nimesulide | 600 ppm/high fat diet | 80 d | 1 | | | 20 | 100 | 37 |
| NSAID/2 | ONO-AE2-227 | 300 ppm | 7 w | 1 | 61 | 0.5 | 69 | 40 | 56b |
| NSAID/2 | Rofecoxib/Apc716 | 25–75 ppm | 8 w | 2 | 201 | | 55 | | 53 |
| Other | Beef meat | 24% | 5–6 w | 1 | 35 | 1.8 | 150 | 178 | 22 |
| Other | Bovine lactoferrin | 0.2% or 2% | 8 w | 1 | 54 | 1.2 | 82 | 83 | 57 |
| Other | Citrobacter rodentium | 10E8 cfu one gav. | 152 d | 1 | 9 | 0.8 | 79 | 350 | 58 |
| Other | Copper | 6 vs 1 ppm | 13 w | 1 | 47 | 1.0 | 46 | 27 | 59 |
| Other | DSS | 4% in water | 4 or 8 d | 2 | | 1.7 | | 1421 | |

| | | | | | | | | | |
|-------------|--------------------------|------------------------|------------|---|-----|-----|------------|-------------|----|
| | | | | | | | | | 60 |
| Other | Exercise | 1.2km/1h/d | 7 w | 1 | 37 | 3.2 | 89 | 75 | 61 |
| Other | Food restriction | 20% restriction | 7 w | 1 | 55 | 2.3 | 93 | 48 | 62 |
| Other | Germ-free status | germ-free | 85 d | 1 | 32 | 1.4 | 88 | 66 | 63 |
| Other | Methionine | 0.7% | 4 w | 1 | 26 | 0.5 | 96 | 180 | 64 |
| Other | PEG 3350 | 10% | 10 w | 1 | 42 | 3.2 | 53 | 81 | 65 |
| Other | PEG 8000/MinMsh2+or- | 5% in male&fem. | 60 d | 1 | 12 | 0.0 | 104 | 3020 | 66 |
| Other | Selenium in broccoli | 2.1 ppm Se | 10 w | 1 | 67 | 1.9 | 71 | 22 | 67 |
| Other | Selenium p-XSC | 10–20 ppm | 80 d | 2 | 41 | 2.8 | 58 | 43 | 68 |
| Other | Sphingomyelin -ceramides | 0.1% | 8 w | 3 | 56 | 1.4 | 56 | 50 | 69 |
| Other | Uroguanylin | 26 µg/mouse/d | 11 w | 2 | 48 | 0.7 | 57 | 14 | 70 |
| Other | Vegetables & fruits mix. | 20% mix in 9%fat diet | 110 d/d-20 | 2 | 17 | 1.5 | 82 | 152 | 71 |
| Other | Vegetables & fruits mix. | 22% mix in 20%fat diet | 110 d/d-20 | 2 | 17 | 1.5 | 162 | 152 | 71 |
| Phytochem | Acarbose/Apc1309 | 400 ppm | 10 w | 1 | 31 | 2.6 | 93 | 84 | 47 |
| Phytochem | BB protease inhib. | 0.1–0.5% | 92 d/d-2 | 2 | 11 | 0.6 | 63 | 67 | 72 |
| Phytochem | Caffeic CAPE | 0.15% | 75 d | 1 | 33 | | 37 | | 73 |
| Phytochem | Catechin (+) | 0.1–1% | 75 d | 2 | 26 | 0.6 | 27 | 17 | 74 |
| Phytochem | Curcumin | 0.2% | 10 w | 1 | 14 | | 94 | | 75 |
| Phytochem | Curcumin | 0.1% | 75 d | 1 | 33 | | 36 | | 73 |
| Phytochem | Lignan HMR | 200 ppm/inulin diet | 5–6 w | 1 | 40 | 1.3 | 67 | 131 | 28 |
| Phytochem | Resveratrol | 100 ppm in water | 7 w | 1 | 30 | 4.0 | 30 | 0 | 76 |
| Phytochem | Rutin-quercetin | 2% | 75 d | 2 | 33 | | 85 | | 73 |
| Phytochem | Soy isoflavones | 475 ppm vs 16 ppm | 11 w | 2 | 31 | | 99 | | 77 |
| Phytochem | Tea extr. +sulindac | 0.1% water +300ppm | 10 w | 1 | 72 | | 44 | | 52 |
| Phytochem | Tea extract (green) | 0.1% iwater | 10 w | 1 | 72 | | 78 | | 52 |
| PPAR activ. | BRL49,653 | 20 mg/kg/d | 8 w | 1 | 27 | 0.6 | 113 | 525 | 78 |
| PPAR activ. | Troglitazone | 150 mg/kg/d | 8 w | 1 | 22 | 0.6 | 104 | 283 | 78 |
| PPAR activ. | Troglitazone | 0.2% | 5 w | 1 | 67 | 1.0 | 116 | 300 | 79 |
| Vitamin B | Folate | 8–20 ppm | 13 w/w3 | 2 | 24 | 4.6 | 80 | 80 | 80 |
| Vitamin B | Folate | 2-8-20 ppm | 26 w/w3 | 3 | 18 | 2.6 | 126 | 120 | 80 |
| Vitamin B | Folate/MinMsh2-- | 8 ppm | 8 w/w3 | 1 | 299 | 1.7 | 37 | 35 | 81 |
| Vitamin B | Folate/MinMsh2-- | 8 ppm | 5 w/w6 | 1 | 70 | 2.4 | 422 | 100 | 81 |
| Vitamin B | Folate + choline | 2 ppm+3% vs 0+1.4 | 70 d/d21 | 3 | 29 | | 114 | | 82 |

| | | | | | | | | | |
|-----------|----------------|----------------|------|---|----|-----|-----|-----|----|
| Vitamin D | 1a,25 (OH)2-D3 | 3 × 0.01 µg/wk | 10 w | 1 | 17 | 4.5 | 108 | 89 | 51 |
| Vitamin D | Ro 26-9114 | 3 × 5 µg/wk | 10 w | 1 | 17 | 4.5 | 102 | 104 | 51 |

Notes to table 1:

a Mutation(s) given when different from the Apc850 mutation (Min mouse)

b ppm, part per million; % of diet; mg/kg of body weight; inj., injection; gav., gavage.

c w, weeks; d, days; Treatment start:/w1: from one w after birth;/d-20: from 20 d before birth.

d Number of similar studies from the same article which were pooled before reporting mean value.

e Number of adenomas in the small intestine of control mice (some studies report total number of intestinal adenomas), and in their colon.

f Number of adenomas in treated mice, reported as percent of number in control mice (% smaller than 100 denotes protection). Boldface: significant effect (either decrease or increase).

Table 2

Agents with a very different effect on the tumor number in the small intestine and in the colon of Min mice (ratio below 0.4, or above 2.5, data from Table 1).

| Category | Treatment | N ^a | Treatment effect in the colon: treated % control | Protection ratio: effect in small intestine vs colon | Ref. |
|-------------|-------------------------|----------------|--|--|------|
| NSAID | Sulindac | 1 | 25 | 0.04 | 49 |
| NSAID | Sulindac | 1 | 33 | 0.22 | 50 |
| NSAID | Piroxicam | 3 | 150 | 0.15 | 44 |
| NSAID | Piroxicam | 1 | 169 | 0.20 | 45 |
| NSAID/2 | Celecoxib | 1 | 253 | 0.19 | 45 |
| NSAID/2 | Nimesulide | 1 | 100 | 0.20 | 37 |
| PPAR activ. | BRL49,653 | 1 | 525 | 0.22 | 78 |
| PPAR activ. | Troglitazone | 1 | 283 | 0.37 | 78 |
| PPAR activ. | Troglitazone | 1 | 300 | 0.39 | 79 |
| inhib. iNOS | Arginine deficient diet | 1 | 300 | 0.22 | 36 |
| Fiber | High fiber chow | 1 | 271 | 0.35 | 23 |
| Fiber | Wheat bran | 2 | 143 | 0.37 | 23 |
| Fat | Fish oil K85 | 1 | 160 | 0.20 | 21 |
| Other | Citrobacter rodentium | 1 | 350 | 0.23 | 58 |
| Other | PEG 8000 | 1 | 3020 | 0.03 | 66 |
| Fiber | Fructo-oligosaccharide | 1 | 33 | 2.8 | 25 |
| Other | Selenium in broccoli | 1 | 22 | 3.2 | 67 |
| Other | Uroguanylin | 2 | 14 | 4.0 | 70 |
| Vitamin | Folate/MinMsh2-- | 1 | 100 | 4.2 | 81 |
| inhib. iNOS | PBIT | 1 | 10 | 6.6 | 37 |
| Phytochem | Resveratrol | 1 | 0 | 100 | 76 |

a Note: see abbreviations and notes to Table 1.

Table 3

Summary of dietary prevention of colorectal tumors in rats, mice and humans

Value in treated group percent of control group.

| Agent or Diet ^a | AOM-rats, colon tumor incidence ^b | Min mice, polyp number, | | Human trial, polyp recurrence | References and notes |
|----------------------------|--|-------------------------|---------------|-------------------------------|----------------------|
| | | Small bowel | Large bowel | | |
| Selenium | 50 (7) ^c | 60 (3) | 40 (3) | 50 | 99 d |
| Celecoxib | 20 (2) | 60 (4) | 110 (6±) | 70 | 100 e |
| Aspirin | 90 (9±) | 70 (4) | 70 (2) | 80 | 101 f |
| Sulindac | 60 (8) | 50 (15) | 70 (7±) | 80 | 102 g |
| Calcium | 70 (6±) | | | 80 | 24 h, 103 |
| Wheat bran | 60 (9) | 80 (4) | 90 (4±) | 90 | 104 |
| Low fat | 80 (10±) | 70 (1) | 50 (1) | 100 | 105_108 i |
| Caloric reduction | 50 (3) | 90 (1) | 50 (1) | 100 | 106_108 j |
| Fruits & vegetables | 100 (8) | 120 (4±) | 150 (2) | 100 | 106, 109_111 |
| Beta-carotene | 80 (3) | | | 110 | 108, 112 |
| Vit. C + vit. E | 100 (11) | | | 110 | 112_114 |
| Psyllium | 40 (1) | | | 160 | 115 |

Notes to table 3.

a Tested in clinical trials, ranked by efficacy in humans.

b Null and negative rats' studies were added to a previously review of positive studies (¹⁵).

c Data are mean percentages of colorectal tumor incidence in treated group vs. control group, rounded to the nearest ten (100= no effect). **Boldface**: significant effect; *Italics*: value not firmly established (single or small size trial, secondary endpoint); Within parentheses: number of pooled studies; ±: discrepant studies in the pool.

d Colon cancer was a secondary endpoint in the selenium trial, primarily designed to reduce prostate cancer.

e Polyp reduction shown in FAP patients. No data yet published on sporadic polyps.

f Significant effect of low dose of aspirin (80 mg/d), no effect of high dose (325 mg/d).

g Sulindac shows significant protection in FAP patients (3 small-size trials), not on sporadic polyps (2 trials) (⁴).

h The low-calcium "Western Diet" increases by +175% the tumor yield in Apc1638 mice, but result was not included in Table 3 because it is also a low-vit.D and high-fat diet.

i Significant effect in F344 rats, but no effect in SD rats (not shown). In volunteers, the interventions were in part, or led to, a dietary fat intake reduction.

j The above cited low-fat interventions also led to a reduction of caloric intake, estimated as -18%, -10% and -5% respectively.