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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/corpet. 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.

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.

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 metastize.

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 end-point, 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/corpet.
To the Editor and Reviewers*: Before the present manuscript is accepted, Table 1 can be viewed at a temporary address* ***http://corpet.free.fr*** *(instead of the above mentioned URL).*

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 phenetyl 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 *Apc*716 mutations (Table 1). In addition, sulindac treatment significantly increased colonic tumors in four mutated mouse models: *Apc* Min, *Apc*1638, *Apc*1638/*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 insuline 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: ursodeoxy-cholate, 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 phenetyl 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.

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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 /*Apc*716	3% female	7 w	1	219		**31**		20
Fat	DHA /*Apc*716	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 /*Apc*1638	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- /*Apc*716	bran:fat 20:5 vs 3:20%	7 w	1	211	2.0	**64**	**36**	29
HAA	IQ /*Apc*716	300 ppm	11 w	1	254		84		30
HAA	MeIQx /*Apc*716	400 ppm	11 w	1	254		87		30
HAA	N-OH-PhiP /*Apc*716	50 mg/kg x 5 inj.	5 d /d26	1	17		**335**		30
HAA	PhiP	50 mg/kg x 8 inj.	pups 3 w	1	30	0.6	**789**	**519**	31
HAA	PhiP	25 mg/kg x 8 inj.	pups 3 w	1	30	0.6	**524**	145	31
HAA	PhiP	50 mg/kg x 1 inj.	7-11 w	2	47	0.6	**346**	**297**	32
HAA	PhiP	10 mg/kg x 1 inj.	7-11 w	2	47	0.6	**188**	157	32
HAA	PhiP	50 mg/kg x 4 inj.	4 w	2	72	0.7	108	78	33
HAA	PhiP /*Apc*1638	0.03% male&fem.	182 d	1	3		**234**		34
HAA	PhiP /*Apc*716	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 balzalazide	250 mg/kg ?	90 d	1	22		**28**	21	41
NSAID	5-ASA balzalazide	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 /*Apc*1309	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 /*Apc*716	150 ppm	8 w	1	201		**62**	100	53
NSAID	Sulindac /*Apc*716	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 /*Apc*716	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 /*Apc*716	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 /*Apc*1309	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 x 0.01 µg/wk	10 w	1	17	4.5	108	89	51
Vitamin D	Ro 26-9114	3 x 5 µg/wk	10 w	1	17	4.5	102	104	51

Notes to table 1:

a: Mutation(s) given when different from the *Apc*850 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 /Min*Msh*2--	1	100	4.2	81
inhib. iNOS	PBIT	1	10	6.6	37
Phytochem	Resveratrol	1	0	100	76

Note: a: 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 *Apc*1638 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.

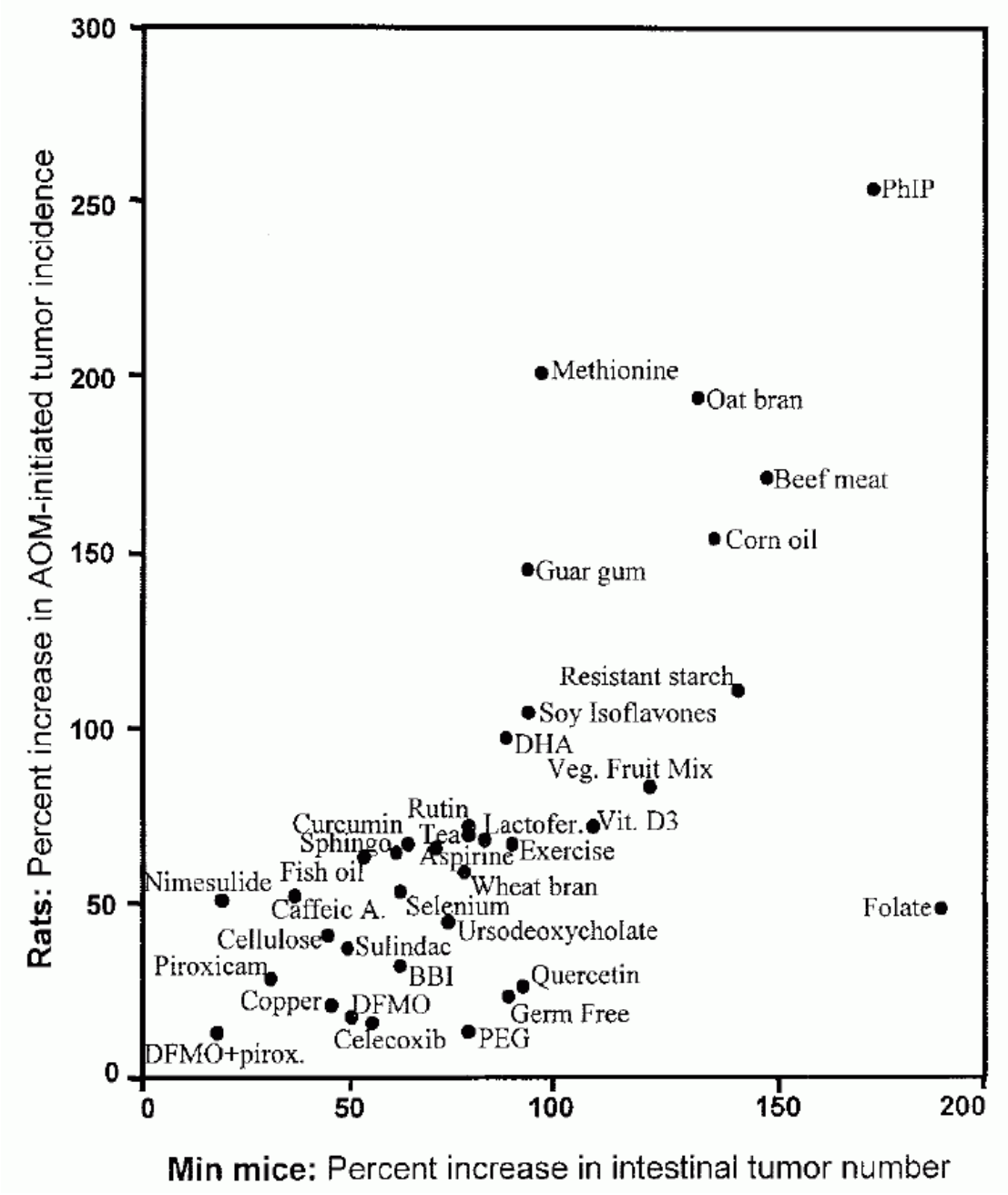

Figure 1. Correlation between the effect of various agents on the number of adenomas in Min mice small intestine and on the incidence of colon tumors in AOM-initiated rats.

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).