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REVIEW

Most Effective Colon Cancer Chemopreventive Agents in Rats: A Systematic Review of Aberrant Crypt Foci and Tumor Data, Ranked by Potency.

Denis E. Corpet, and Sylviane Taché.

Abstract: *Potential chemopreventive agents for colorectal cancer are assessed in rodents. We speculated that the magnitude of the effect is meaningful, and ranked all published agents according to their potency. Data were gathered systematically from 137 articles with the aberrant crypt foci (ACF) endpoint, and 146 articles with the tumor endpoint. A table was built containing potency of each agent to reduce the number of ACF. Another table was built with potency of each agent to reduce the tumor incidence. Both tables are shown in the present paper, and on a website with sorting abilities (http://www.inra.fr/reseau-nacre/corpet). Potency was estimated by the ratio of value in control rats divided by value in treated rats. From each article, only the most potent agent was kept, except from articles reporting the effect of more than 7 agents. Among the 186 agents in the ACF table, the median agent halved the number of ACF. The most potent agents to reduce azoxymethane-induced ACF were pluronic, polyethylene glycol, perilla oil with beta-carotene, and sulindac sulfide. Among the 160 agents in the tumor table, the median agent halved the tumor incidence in rats. The most potent agents to reduce the incidence of azoxymethane-induced tumors were celecoxib, a protease inhibitor from soy, difluoromethylornithine with piroxicam, polyethylene glycol, and a thiosulfonate. For the 57 agents present in both tables, a significant correlation was found between the potencies against ACF and tumors (r=0.45, p<0.001). Without celecoxib, a major outlying point in the correlation, it reached r=0.68 (p<0.001, N=56). In conclusion, this review gathers almost all known chemopreventive agents, ranks the most promising ones against colon carcinogenesis in rats or mice, and further supports the use of ACF as surrogate endpoint for tumors in rats.*

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The abbreviations used are: ACF, aberrant crypt foci; DFMO, difluoromethylornithine; MMTS, S-methyl methane thiosulfonate; NSAID, non-steroidal anti-inflammatory drug; PEG, polyethylene-glycol; The abbreviations used only in the tables are given in a note to Table 1.

Introduction

Dietary changes might prevent 70-80% of colorectal cancer, a major cause of death in nonsmokers (1). Diet may carry chemopreventive agents that could reduce the cancer risk. These agents can inhibit the initiation of preneoplastic lesions by carcinogens, or reverse their progression to invasive cancers. More than 300 agents have been tested in rodents: most of them were fed to rats, during or after the injection of a colon carcinogen. The aim of those animal studies is to detect potent and non-toxic chemopreventive agents that might eventually be given to people, to reduce their risk of colorectal cancer.

Few agents have indeed been tested in randomized double-blinded human trials. Most tested agents showed no preventive effect: the risk of polyp recurrence was not reduced in volunteers fed for years with supplements of wheat bran, vitamin E and C, beta-carotene, or psyllium (2-7), or induced to eat less fat or more fruits and vegetables (6-8). Supplemental calcium decreased by 15-20 % the polyp recurrence in volunteers (9). Celecoxib, a NSAID, decreased by 30% the number of polyps in FAP patients (10). In addition, other human intervention studies showed a preventive effect of selenium, sulindac, ursodeoxycholic acid, N-acetylcysteine, or lactulose. But these studies were not definite: colon tumors were not the primary endpoints, the number of patients was small, or the treatment was not double-blinded (11-15). Clearly, no agent is yet ready for colon cancer chemoprevention in humans, except, may be, calcium and celecoxib.

Before 1990, the gold standard endpoint for chemoprevention in rodents was the incidence of macroscopic tumors: colon adenomas and adenocarcinomas induced by a chemical carcinogen. These endpoints are clearly related to cancer, but have three major drawbacks: (i) a tumor requires a long time to develop (usually 5-8 months), (ii) each tumor must be confirmed by histology, which is long and costly, and (iii) each animal brings little information to the study (each rat has either no tumor or a tumor), thus large groups of rats are needed for statistical analysis. In 1987, Bird described putative precursors of colon cancer, aberrant crypt foci (ACF), first detected in rodents few weeks after carcinogen injection (16). The crypts in ACF are easy to score on whole mount colon: they are two to three times larger than normal crypts, are microscopically elevated, have a slit-like opening, a thick epithelial lining that stains darker than normal crypts

with a large pericryptal zone (17). It was demonstrated that: (i) ACF were induced by all colon carcinogens in a dose- and species-dependant manner; (ii) their number and growth were modified by the modulators of colon carcinogenesis, and they predicted the tumor outcome in several rodent studies; (iii) they correlate with colon cancer risk, and adenoma size and number in humans; (iv) the morphological and genotypic features of ACF in human colons were similar to those in animal colons, and many alterations are similar in ACF and in tumors; (v) some ACF show dysplasia, and carcinoma were observed in rodents and humans' ACF (18-19). The use of the ACF system to study modulators of carcinogenesis has accelerated for the last 10 years, for it provides a simple and economical tool for preliminary screening of potential chemopreventive agents, and it allows a quantitative assessment of the mechanisms of colon carcinogenesis (20). However, the preneoplastic nature of ACF is controversial, and other premalignant lesions were recently described in the rat colon (21).

The major goal of this study was to point out the most potent chemopreventive agents already published. To reach this goal, we had three minor aims:

(i) to gather all published studies on the effect of dietary chemopreventive agents against colon carcinogenesis in rats (or mice) after carcinogen injection,

(ii) to rank the agents, according to their potency to inhibit colon ACF on the one hand, and colon tumors on the other hand. Ranking is a critical step that can help to set priorities when selecting agents for human trials. These ranked lists could be used to choose an agent provided it is not toxic. This attempt is similar to the ranking of carcinogenic hazards published by Ames and Gold (22)

(iii) to test the hypothesis that the potencies of agents in the ACF assay and in the tumor assay are correlated.

Materials and Methods.

All publications on the effect of dietary chemopreventive agents against colon carcinogenesis in rodents, and cited in the Current Contents Life Science from January 1989 to December 2001, were obtained from their authors. In addition, searches were done on the Medline data base, and on the web sites of the American Association for Cancer Research, and of the journals *Carcinogenesis* and *Cancer Letters*. Studies of specific agents were collected, as well as dietary studies. Each article was carefully read, and seven of them were rejected due to low plausibility. In addition, some engaging articles do not report suitable quantitative data (e.g., 23-25). We did not include obvious toxic agent, e.g., methylcholanthrene (26). Articles reporting non-significant protection, or a promoting effect, were not included either.

Because our goal was to point out the most potent chemopreventive agents, we kept only the single most potent agent and dose from each article. However, some articles deal with many agents (e.g., 27). From the thirty articles dealing with more than seven agents, we kept more than one agent. From each study, we decided to keep the most potent agent out of seven. In other words, we kept the top 14 percent agents from large studies. We inferred data from the height of the bars, when the original paper gives a histogram instead of a table.

Data were gathered from 137 articles with the ACF endpoint, yielding 186 ACF preventive agents (because two or more agents were kept form articles dealing with more than seven agents). A primary ACF table (not shown) was built containing the mean number of total ACF per colon, of large ACF per colon, and of crypts per ACF in each group of rats (control and treated). In most studies, a "large ACF" contains four or more crypts. Data were also gathered from 146 articles with the tumor endpoint, yielding 160 tumor preventive agents or diets. A primary tumor table (not shown) was built with the incidence of tumors, the incidence of invasive carcinomas, and the mean tumor multiplicity in each group of rats (control and treated). Data from each article were double-checked by the second author, independently from the first one.

A potency index was then estimated for each agent in each study, by calculating the ratio of mean value in control rats divided by mean value in treated rats. For instance, in the Wargovich's study (27), a mean number of 193 ACF was observed in control rats, and of 28 ACF in rats given sulindac sulfide: the potency of sulindac sulfide to reduce the ACF number was calculated as 193/28 = 6.89. As an other example, in the Corpet's study (28), the incidence of tumors (confirmed by histology) was 22/27 in the control group, and 2/21 in the group of rats given polyethylene glycol (PEG): the potency of PEG to reduce the tumor incidence was calculated as (22/27)/(2/21) = 8.55. Thus, potency tells the times-fold reduction in a carcinogenesis endpoint due to the agent. When incidence is concerned, potency is the inverse of the relative risk (e.g., a potency of 8.55 corresponds to a relative risk of 0.12). This article reports ACF and tumor potency tables (tables 1 and 2). In addition, to help the reader, some endpoints were also reported as percent inhibition afforded by the agent, which is equal to 100 - 100/potency (e.g., a potency of 8.55 gives a 88.3% inhibition). When no tumor was seen in the control group, potency calculation was arbitrarily based on 0.5 tumors in the group. Our potency estimate does not take in account the dose used. We chose not to include the dose in the potency calculation, because most treatments were close to the maximum tolerated dose (40 or 80%): the authors often used the highest possible dose they could, to get the maximum protection. For instance, non-toxic agents like dietary fibers can be included in both rodent and human diets at a much higher level than agents that are more toxic and possibly more potent to prevent cancer (e.g., selenium, retinoids, and NSAIDs). The experimental design of each study was recorded, but not fully shown here: the animal species and strain, the initiating carcinogen and doses, the treatment dose and duration. If the agent was given during the time of exposure to the carcinogen, the protocol was labeled "init" for initiation, if it was given after initiation, the label was "post" for post-initiation. In most studies, the agent was given to rats during both periods (during and after the carcinogen): these protocols were labeled "both." The post-initiation protocol has more clinical relevance since it may identify agents that prevent the recurrence and progression of precursor lesions for colon cancer (27). Most studies were done in rats initiated with dimethylhydrazine or its metabolite azoxymethane (237/283). We also chose to include in this review the few chemoprevention studies done with carcinogens different from dimethylhydrazine or azoxymethane (24/283), and the studies done in the mouse (22/283), because some promising agents were tested only in the mouse (e.g., protease inhibitor, sphingomyelin).

Each agent was classified within a class of agents,

according to its chemical structure, its supposed mechanism, or its origin. We chose the following nine classes: amines modulators and DFMO; calcium and other mineral salts; fibers and bacteria; lipids; NSAIDs; PEGs; phytochemicals; vitamin A, D and retinoids; others.

Both tables are printed here, and are also available on a website with sorting abilities. Large printed tables are hard to scan for a specific agent: the website helps the reader to fetch all studies on a specific agent; In addition, the electronic table enables the reader to rank the agents according to their potency to decrease any endpoint, and to sort data by class of agents or by design protocol.
http://www.inra.fr/reseau-nacre/sci-memb/corpet/indexan.html

Correlation between ACF and tumor enpoints was calculated and plotted, for the 57 agents that were present in both ACF and tumor tables, using the Systat 5.03 software (Systat inc., Evanston, IL). Independent studies with the same agent were not averaged, but each was included in correlation calculation. A second attempt to calculate correlation was made with the median potency obtained for each agent in different studies. However, both calculations gave exactly the same r value.

Results

Table 1 shows the efficacy of chemopreventive agents on ACF endpoints. The agents were ranked according to their potency to reduce the number of ACF per rat. Most potent agents are thus placed on the top of the table, and eleven articles report agents that reduce the ACF number by more than 80% (potency higher than 5). The most potent agents were pluronic (potency 76, i.e., pluronic treatment reduced 76-fold the ACF number), PEG (potencies of 56, 18, 14, 8 and 5.5 in five independent articles), perilla oil associated with beta-carotene (potency 11), indole-carbinol (potency 11 on imidazopyridine-induced ACF, but control rats had only 3 ACF/rat), a NO-releasing aspirin derivative (potency 7 on TNBS-DMH-induced ACF), sulindac sulfide (potency 7), and a caffeic acid ester (potency 5.6). Among the 186 agents in the ACF table, the median agent halved the number of ACF (median potency, 2). Indole-carbinol, PEG (three studies), chlorophillin, cork, pluronic, sanshishi, auraptene (two studies), troglitazone, zerumbone, ursodeoxycholic acid and hesperidin were the most potent agents to reduce the ACF size (or crypt multiplicity), a marker of the ACF growth rate. As shown in table 1, each agent was attributed to a class (last column). The mean potencies of all agents in each class on ACF were calculated, compared by ANOVA analysis, and shown on figure 1 as percent inhibitions (hatched bars). PEG class was significantly more potent than any other class (ANOVA $p<0.0001$). No significant difference was seen among the eight other classes (PEG-omitted ANOVA $p=0.28$).

Table 2 shows the efficacy of chemopreventive agents on tumor endpoints. The agents were ranked according to their potency to reduce the incidence of tumors in the colon and rectum. Sixteen articles report agents that reduce the tumor incidence by more than 80% (potency higher than 5). The most potent agents were celecoxib (potency 15), piroxicam or aspirin with DFMO (potencies 9 or 5.3), PEG (potencies of 8.6 and 7 in two independent articles), S-methyl methane thiosulfonate (MMTS, potency 7.9), *Bifidobacterium longum* (potency higher than 7 against imidazoquinoline initiation), a protease inhibitor (potency 10.4 and estimated 7.3 in two mice's studies), folic acid (potency 7), piroxicam (potency 6.5), pectin (potency 5.7), obacunone (potency 5.5), and magnesium hydroxide (potency 5.3). Most of these agents were included in the diet during both initiation and promotion phases, and only PEG, MMTS, piroxicam, and obacunone were effective after the end of the initiation period (protocol labeled "post" in table 2). Some potencies were not accurately established, because the tumor incidence was small in the control group. It was often the case for the most potent agents. Indeed, potency of *B. longum,* protease inhibitor, folic acid, and calcium glucarate, were based on only 7 tumor-bearing rats or mice in their respective control group (see table 2, column 5).

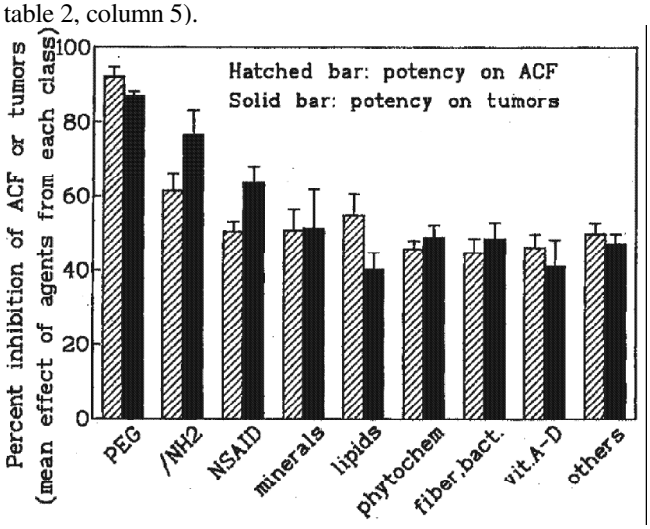

Figure 1. Mean potency of all chemopreventive agents in each class to reduce number of aberrant crypt foci (ACF) and tumor incidence in colon of rats. Nine classes are as follows: polyethylene glycol (PEG), difluoro-methylornithine and amine modulators (/NH2), nonsteroidal anti-inflamma-tory drugs (NSAID), calcium and other mineral salts, lipids (mostly n-3 polyunsaturated fatty acids), phytochemicals and plant extracts (phytochem), fibers and bacteria, vitamins A and D and retinoids, and others. Bars, mean percent inhibition of treated group compared with control group; error bars, SEM.

Among the 160 agents in table 2, the median agent halved the tumor incidence (median potency, 2). No carcinoma was detected (100% inhibition of cancer) in rats fed ursodeoxy-cholic, PEG (two independent studies) or MMTS, and in rats given exercise. In addition, celecoxib, acetoxychavicol, selenium, p53 vaccination, piroxicam with DFMO, cellulose, aspirin, S-allylcysteine, obacunone, sulindac sulfone and hesperidin (two studies) reduced the incidence of adenocarcinoma more than 78%. Each agent was attributed to one of nine classes, as in table 1. The mean potency of agents in each class were calculated, compared by ANOVA analysis, and shown on fig. 1 as percent inhibition of the tumor incidence (solid bars). The mean potency of NSAIDs, PEGs, and amine modulators were not different, but PEG class was significantly more potent than the six other classes (ANOVA $p=0.0004$). When PEG was omitted, the ANOVA remained significant ($p=0.02$), but NSAIDs and amine modulators were not significantly more potent than any of the other classes (all pairwise p were larger than 0.05).

In an attempt to combine results from both tables, we merged the six tabulated endpoints in a non-parametric way. Tables 1 and 2 were ranked sequentially according to potency of each agent to reduce (i) the number of ACF, (ii) the number of large ACF, (iii) the number of crypts per ACF, (iv) the tumor incidence, (v) the adenocarcinoma incidence, and

(vi) the tumor multiplicity. Obviously, these endpoints are partly redundant, but they do not fully overlap. We gathered the top-twenty agents against each endpoint in a list of 120 items (not shown). Agents cited most often in this list were then PEG 8000 (cited 20 times), DFMO alone or with piroxicam or aspirin (8 times), a protease inhibitor (5 times), celecoxib, hesperidin, sulindac sulfone or sulfide, and *Bifidobacterium* (4 times each). Other agents appeared 3 times or less in the table: they may be potent agents too, but have been reported in few articles yet. Making the list with top-12 agents instead of top-20 did not change much the most-cited agent list.

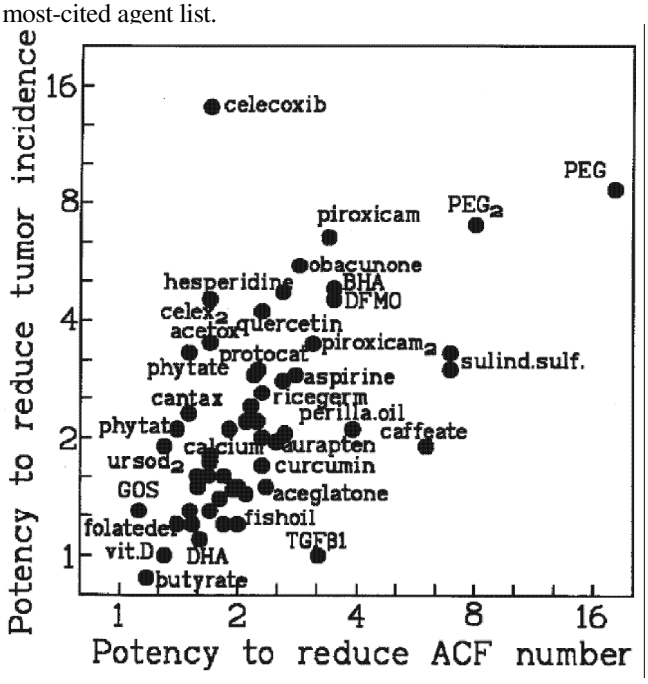

Figure 2. Correlation between potency of each agent to reduce number of ACF and to reduce incidence of tumors in colon of rats. Data from Tables 1 and 2 are shown on logarithmic scales. Points between 1.5 and 3 were too tight to be labeled. GOS, glucooligosaccharide; TGF-β_1, transforming growth factor-β_1; BHA, butylated hydroxyanisole; DFMO, difluoromethylornithine; DHA, docosahexaenoic acid.

Fifty-seven agents were found in both table 1 and 2. A significant correlation was found between the potencies in the ACF assay and in the tumor assay ($r=0.45$, $N=57$, $p<0.001$). As shown on fig. 2, celecoxib is very potent against tumors, but not against ACF. It thus appeared as a major outlier in the tumor-ACF correlation. When this outlying point was dropped, correlation increased to $r=0.68$ ($N=56$, $p<0.001$). The faster ACF grow, the larger they become. Thus the ACF size may relate more closely to the tumor endpoint than the ACF number (160, 293, 294). However, many articles do not report ACF size or large ACF number, and correlation could be calculated from fewer points than above. Correlation of the tumor incidence with ACF multiplicity was $r=0.69$ ($p=0.005$, $N=20$), and with the number of large ACF was $r=0.76$ ($p<0.001$, $N=36$).

Discussion

This review of the literature proposes a ranking of the most potent agents detected in rodents' studies, and supports the notion that ACF may be used as a surrogate endpoint for tumors in rats. We will discuss possible bias in the ranking (publication bias and selection process bias) before showing possible extensions of the work. We will then discuss correlation between ACF and tumor, also looking for bias, trying to explain the outlying point, and concluding that ACF may be used as surrogate endpoints. We will not discuss here the mechanisms of inhibition, already addressed in reviews (e.g., 295, 296).

By combining six carcinogenesis endpoints from tables 1 and 2, this review suggests that the most potent agents are PEG 8000, a protease inhibitor, DFMO alone or with piroxicam or aspirin, hesperidin, celecoxib, sulindac sulfone or sulfide, and *Bifidobacteria* strains. One may prefer to rely on a single endpoint (e.g., cancers), which would result in a slightly different list (Table 2). Our non-parametric ranking takes in account both the potency of the agent, and the number of studies published on it. This may be seen as a publication bias, but it is also a measure of the strength of the evidence. We think the most potent agents cited above are promising for cancer prevention, and should be tested in people at risk. However, agents with low potency can also be valuable, particularly those that are naturally present in foods. We like better the idea to prevent cancer by eating intact plant food with the multiplicity of agents that they contain, than by packaging potent anticarcinogenic constituent in a daily pill. However, up to now, we have no direct evidence that the first approach is efficient.

It is likely that this review missed some articles, particularly those published before 1989 and very recent ones. However, we think that no potent agents could be missed: the early comprehensive review of Angres and Beth (297) points out the protective effect of wheat bran, cellulose, low fat, selenium and caloric restriction. Each of these factors is cited several times in table 2, but we did not report all early studies. For instance, although we reported many studies on the chemoprevention by fish oil or by n-3 fatty acids, only five studies on low-fat diet were included. One reason is that a low-fat diet is not exactly a "chemopreventive agent." Another reason is that the protection afforded by low-fat diets is often small. Indeed, a meticulous review of 14 studies of dietary fat and rat colon carcinoma shows that fat has no effect in one study out of two (298). Specifically, no association between colon cancer incidence and fat intake is seen for Sprague-Dawley rats, but a positive relationship is indicated for Fischer 344 rats. When the degree of saturation is taken into account, only n-6 polyunsaturated fat intake significantly promotes the cancers. We used the logistic regression analysis from the quantitative review (298), to calculate the "potency" of a low-fat diet to reduce the cancer incidence in Fisher 344 rats. Compared with a high-fat diet (20% fat), the median potency of a low-fat diet (5% fat) to reduce the cancer incidence was 1.3, which is in the bottom-ten of table 2.

Because our first aim was to find the most potent agents against colon carcinogenesis, we used a selection process to build the tables. The result could thus mislead the reader for some agents:

(i) Some potent agents are not shown in the tables because they were hidden by a more potent one in the same article. This is the case, for instance, of limonin. This citrus limonoid was reported in the same article as obacunone (54). Both were very potent to prevent ACF and tumors, but we dropped limonin since obacunone was more potent.

(ii) Some agents rank very high in the tables, but are less potent in duplicated studies. For instance, MMTS reduces 8-fold the tumor incidence in a first study (170), but has little effect (1.1-fold reduction) in a duplicated study (285).

(iii) Some agents might have been dropped from the tables, if negative studies had been taken in account too, and if mean potencies have been calculated for each agent. For instance, a specific nitric oxide synthase inhibitor prevents colon carcinogenesis (147), but can also promote carcinogenesis (299). Similarly, many agents shown here as preventive, did enhance carcinogenesis in other rat studies (e.g., beta-sitosterol, benzyl- and phenylhexyl- isothiocyanates, calcium, cellulose, diallyl sulfide, folic acid, genistein, germfree status, glucarate, pectin, quercetin, resistant starch, rutin, selenium, tea extracts, vegetables and fruits mixture, and vitamin D3). Thus, the tables may help to find the most potent agents, but cannot be used to calculate the average effect of a given agent.

The present work could be extended in four directions:

(i) The tables could be updated when new agents are published. We propose to do this on a website with sorting abilities (http://www.inra.fr/reseau-nacre/corpet).

(ii) It could be useful to have a comprehensive view of all the studies on colon cancer chemoprevention in rodents. Thus, all results from each paper should be included in the tables, including less potent agents and those that promote carcinogenesis. This would allow the calculation of the mean potency of each agent. However, since most negative results are not published, a large publication bias would be inevitable. We decided not to do this in the present article, to produce tables of reasonable size.

(iii) Many agents have also been tested in the Min mouse model, or similar models (e.g., truncated Apc, Msh2, Mlh1). The potency of dietary agents to decrease the number of polyps in these mice could be gathered and ranked in a table. Indeed, NSAIDs decrease the number of polyps in the small intestine of mutant mice. But surprisingly, some potent chemopreventive agents against chemically-induced tumors, namely PEG, celecoxib, piroxicam, sulindac, and DFMO can increase the polyp number or size in the **colon** of mutant mice (36, 300-304). The reason for this puzzling discrepancy is not clearly understood. It may be a result of differences in key enzymes in the small and large intestines (305).

(iv) Any decision to test an agent in a human clinical trial should rely not only on the efficacy of the agent, but also on other considerations: lack of toxicity, the paucity of side-effects, acceptability (e.g., no taste), and price. The chemopreventive doses reported in this review are not toxic for rats. It would be useful however to review accurately the human safety of these agents, but this is out of this paper scope.

A significant correlation was found between the potencies in the ACF assay and in the tumor assay (fig. 2). This finding is weakened by a selection bias and a publication bias. This review gathers agents that inhibit ACF or tumors. It does not report null studies, or agents with promoting properties. Thus, the study could not show strong discrepancies between ACF and tumor data. For instance, an agent that reduces the number of ACF, but increases the tumor incidence could not appear in a correlation, e.g., 2-(carboxyphenyl) retinamide (73, 86). Moreover, many negative studies are never published, and this leads to a publication bias that we cannot overcome. However, out of 40 agents, Steele et al. showed that of the 30 agents tested as active in the ACF assay, 21 prevented colon cancer in rats (306). It is thus likely that correlation could remain true, even if discrepant agents were included in the study. Celecoxib is very potent against tumors, but not against ACF. It thus appeared as a major outlier in the tumor-ACF correlation (fig. 2). Three explanations may be given. Celecoxib could inhibit tumors at a late phase of carcinogenesis (182), maybe by reducing angiogenesis in tumors. It would not inhibit the growth of ACF, since they do not require extra-supply of blood. A second explanation is that celecoxib could inhibit the growth of intraepithelial neoplasia near lymphoid aggregates. These lesions may have a high potential to grow to cancers, but do not proturb in the gut lumen, and could not be counted as ACF (307). Last, the celecoxib potency on ACF may have been under-estimated by chance, or the potency on tumor over-estimated, since each value comes from a single study.

The present study does not prove that ACF are true preneoplastic lesions: maybe they never become cancers. Indeed, most of them do not, since the azoxymethane dose that yields one cancer per rat yields 100 to 200 ACF per colon. In contrast, the so-called "ACF min" (308), or the beta-catenin accumulated crypts and ACF (21, 309), may be truly premalignant lesions for colon cancer. However, this study further supports the use of ACF as surrogate endpoint for tumors in rats. Because ACF can be detected easily without tissue sectioning, and because they correlate with the tumor outcome, they could remain a useful biomarker for the screening of agents for chemoprevention.

Finally, we propose that the potency of each new agent, or the result of each new chemoprevention study reported in the literature, should be compared with previously published agents. The present review shows that the median potency of effective agents published so far is two. A new agent that leads to a twofold reduction in the ACF number or in the tumor incidence is thus an average one. In contrast, an agent that reduces the ACF number or the tumor incidence more than fivefold is of outstanding potency.

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Table 1. Ranking of Agents by Chemopreventive Potency to Reduce ACF in Colon of Rats (or Mice) After Initiation With a Chemical Carcinogen

Agent */Carcinogen* [a]	Ref. author, year.	Potency to Reduce ACF No. [b]	%Inhibition of ACF [c]	Potency on Large ACF [d]	Potency on ACF Size [e]	Pro-Tocol [f]	Ro-dent [g]	Class of Agent [h]
PEG-like pluronic F68 5%	29 Parnaud 01	75.7	99	85.0	1.5	post	Rf"	PEG
PEG 8000 5% */MNU*	28 Corpet 00	56.0	98	58.0	2.0	post	Rf'	PEG
PEG 8000 5%	30 Corpet 99	17.8	94	104.0	2.3	post	Rf"	PEG
PEG 8000 5%	29 Parnaud 01	14.0	93	14.0	1.1	post	Rf"	PEG
perilla oil 12%+ B-carotene	31 Komaki 96	11.4	91		1.2	init	Rf'	lipid
Indole3carbinol 0.1% */PhIP*	32 Guo 95	11.0	91	14.0	2.0	init	Rf'	Phyto
PEG 8000 5%	33 Parnaud 99	7.9	87	30.0	1.3	post	Rf"	PEG
NO-aspirin NCX4016 */TNBS*	34 Bak 98	7.0	86			both	Rw'	NSAID
sulindac sulfide 0.3, then 0.1%	27 Wargov. 00	6.9	85	10.0		post	Rf'	NSAID
caffeate PEMC 500ppm	35 Rao Des. 93	5.6	82	21.0	1.0	both	Rf'	Phyto
PEG 8000 5%	36 Naigam. 00	5.5	82	36.0	1.4	post	Rf'	PEG
grape proanthocyanidins 1%	37 Singletary 01	4.3	77	4.6		both	Rs"	Phyto
troglitazone 30mg/kg	38 Kohno 01	4.2	76	5.4	1.4	init	Rf'	other
linoleic CLA 0.5% */IQ*	39 Liew 95	3.9	74		0.9	init	Rf'	lipid
cooking salt 4.4%	40 Masaoka 00	3.9	74		1.0	init	Rf'	miner.
perilla oil 12% vs olive oil	41 Onogi 96	3.9	74		1.1	init	Rf'	lipid
Bifidobact.1.7%+ inuline 5%	42 Rowland 98	3.7	73	2.3		post	Rs	Fibact
butylhydroxyanisole 0.56%	43 Wargov. 92	3.5	71			init	Rf'	other
DFMO 0.4%	43 Wargov. 92	3.5	71			init	Rf'	/NH2
DFMO 0.4%	44 Wargov. 96	3.5	71			init	Rf'	/NH2
piroxicam 400ppm	27 Wargov. 00	3.4	70			post	Rf'	NSAID
sphingomyelin diOH 0.1%/mice	45 Schmelz 97	3.3	70		1.2	post	Mf"	other
sanshishi 2%	46 Fukutake 00	3.3	70		1.5	both	Rf'	Phyto
sphingomyelin 0.1% /mice	47 Schmelz 96	3.3	69		1.5	post	Mf"	lipid
rutin 3%	27 Wargov. 00	3.2	69			post	Rf'	Phyto
TGF-B1 2ng/d	48 Mikhail. 98	3.2	69		1.2	both	Rr'	other
piroxicam 400ppm	27 Wargov. 00	3.1	67			init	Rf'	NSAID
starch vs sucrose-dextrin diet	49 Poulsen 01	3.1	67	11.5		both	Rf'	other
retinoic acid allTrans 190ppm	27 Wargov. 00	3.0	67	3.4		post	Rf'	vit.Ad
wheat bran 20% vs no fibre	50 Ishizuka 96	3.0	67	0.6		init	Rw'	Fibact
glucose vs sucrose bolus /mice	51 Stamp 93	3.0	67			init	Mf"	other
piroxicam 125ppm 12to24wks	52 Morishita 97	2.9	65	3.0		post	Rf'	NSAID
docosahexaenoic 0.5ml/d	53 Takahashi 93	2.9	65		1.2	both	Rf'	lipid
obacunone 200ppm	54 Tanaka 01	2.9	65		1.1	init	Rf'	Phyto
DFMO 0.4%	55 Paulsen 97	2.9	65	6.2		both	Rf'	/NH2
Aspirin 10ppm	56 Mereto 94	2.8	65	3.0	1.2	init	Rs'	NSAID
resistant starch 25%	57 Cassand 97	2.8	65			post	Rs'	fibact
tetracycline 1.25%	27 Wargov. 00	2.8	64			init	Rf'	Fibact
piroxicam 200ppm	58 Wargov. 95	2.8	64	8.0		post	Rf'	NSAID
docosahexaenoic 0.7ml/d/*PhiP*	59 Takahashi 97	2.8	64	3.7	1.1	init	Rf'	lipid
Taurine 1.2ppm	27 Wargov. 00	2.7	64			init	Rf'	other
beet fiber 10% */gamma ray*	60 Nagai 00	2.7	64		0.7	init	Rw'	Fibact
glycyrrhetinic acid 0.5%	41 Wargov. 96	2.7	63			init	Rf'	Phyto
red ginseng 1%	61 Li Wanib. 00	2.7	63	2.1		init	Rf'	Phyto

Table 1. *(Continued)*

Agent */Carcinogen* [a]	Ref. author, year.	Potency to Reduce ACF No. [b]	%Inhibition of ACF [c]	Potency on Large ACF [d]	Potency on ACF Size [e]	Pro-Tocol [f]	Ro-dent [g]	Class of Agent [h]
tannin (red alder) 10mg/kg /mice	62 GaliMuht, 01	2.6	62			init	Mb	Phyto
hesperidin 0.1%	63 Tanaka 97	2.6	62		1.3	post	Rf'	Phyto
beet fiber in 20% lard diet	64 Kristians. 95	2.6	61	1.7		both	Rw'	Fibact
Bifidobacterium 2E8/g	65 Abdelali 95	2.6	61	5.7		init	Rs'	Fibact
selenium BSeSG 3.4ppm	66 Kawamori 98	2.6	61	6.0		both	Rf'	other
lactosylCeramide 250ppm/mice	67 Schmelz 00	2.5	60			post	Mf"	other
PSK vaccine	68 Matsuna. 00	2.5	60		1.0	init	Rf'	other
Indole3carbinol 0.1% */IQ*	69 Xu 96	2.5	59		1.1	both	Rf'	Phyto
tea + milk 3%	70 Weisburg. 97	2.5	59	1.6		init	Rf'	Phyto
WR151327 0.5%	27 Wargov. 00	2.4	58			init	Rf'	other
quercetin 2%	71 Matsuka. 97	2.4	58	3.4		init	Rf"	Phyto
CAI imidazole 200ppm	27 Wargov. 00	2.4	58			init	Rf'	other
aceglatone 2%	72 Yoshimi 01	2.4	58	5.0		init	Rf	Phyto
retinamide 2-CPR 1mol/g	73 Zheng 97	2.3	57	1.5		both	Rf'	vit.Ad
Diallyl sulfide 0.2%	41 Wargov. 96	2.3	57			init	Rf'	Phyto
rice-germ 2.5%	74 Kawabata 99	2.3	57		1.1	init	Rf'	Phyto
curcumin 0.2%	75 Rao Simi 93	2.3	57	4.4	1.0	both	Rf'	Phyto
green tea extract 200ppm	76 Metz 00	2.3	57		1.0	post	Rw'	Phyto
NOS inhibitor PBIT 50ppm	77 Rao Kaw. 99	2.3	57	4.6		both	Rf'	NSAID
auraptene 500ppm	78 Tanaka 97	2.3	56		1.3	post	Rf'	Phyto
sulindac sulfoxide 160ppm	27 Wargov. 00	2.3	56	2.0		post	Rf'	NSAID
ursodeoxycholic acid 0.4%	79 Seraj 97	2.2	55	4.2	1.3	both	Rf'	other
ketyoprofen 200ppm	27 Wargov. 00	2.2	55			post	Rf'	NSAID
D609 150ppm	27 Wargov. 00	2.2	55			init	Rf'	NSAID
selenite 2mg/kg */dmabp*	80 Feng 99	2.2	55		1.0	both	Rf'	other
piroxicam 75ppm	41 Wargov. 96	2.2	55			init	Rf'	NSAID
nobiletin 500ppm	81 Kohno 01	2.2	55	1.9	1.2	both	Rf'	Phyto
selenium broccoli 1ppm */dmabp*	82 Finley 00	2.2	54	1.0		both	Rf'	Phyto
diclofenac 130ppm	27 Wargov. 00	2.2	54			post	Rf'	NSAID
s-allylcysteine 80%MTD	83 Hatono 96	2.2	54			init	R	Phyto
sphingomyelin 500ppm	84 Dillehay 94	2.2	54			?	Mf"	other
lycopene 75ppm	27 Wargov. 00	2.2	54			init	Rf'	Phyto
protocatechuic 0.1%	85 Kawamori 94	2.2	54	1.2	0.8	init	Rf'	Phyto
s-allylcysteine 250ppm	27 Wargov. 00	2.2	53		1.1	init	Rf'	Phyto
retinamide 4-HPR 782ppm	86 Zheng 99	2.2	53			both	Rf'	vit.Ad
Bifidobact.longum lyoph 3%	87 Kulkarni 94	2.1	53	1.7	0.9	init	Rf'	Fibact
arginine 0.5%	44 Wargov. 96	2.1	53			init	Rf'	/NH2
pectin citrus 15%	88 AviviG 00	2.1	53		1.0	both	Rr'	Fibact
sulindac 320ppm	89 Rao New. 98	2.1	53	1.8		both	Rf'	NSAID
retinoic 13cisRet 390ppm	27 Wargov. 00	2.1	53			post	Rf'	vit.Ad
glucarate calcium 5%	27 Wargov. 00	2.1	52			post	Rf'	Phyto
Miso 20%	90 Masaoka 98	2.1	52		0.9	both	Rf'	Phyto
arctiin 200ppm */PhIP*	91 Hirose 00	2.1	51	2.5	1.0	init	Rf'	Phyto
Copper 5 vs 0.8µgCu/g */dmabp*	92 Davis 99	2.1	51			both	Rf'	miner.
ibuprofen 400ppm	44 Wargov. 96	2.0	51			init	Rf'	NSAID

Table 1. *(Continued)*

Agent /*Carcinogen* [a]	Ref. author, year.	Potency to Reduce ACF No. [b]	%Inhibition of ACF [c]	Potency on Large ACF [d]	Potency on ACF Size [e]	Pro-Tocol [f]	Ro-dent [g]	Class of Agent [h]
retinoic 9cisRet 390ppm	27 Wargov. 00	2.0	51			init	Rf'	vit.Ad
lycopene 0.12 mg/d /*MNU*	93 Narisawa 96	2.0	50	2.2		post	Rs"	Phyto
selenium in broccoli 2ppm	94 Finley 01	2.0	50			both	Rf'	Phyto
fish oil 8%	95 Latham 99	2.0	50	2.2		init	Rw'	lipid
retinoic 13cis 780ppm	58 Wargov. 95	2.0	50	1.9		post	Rf'	vit.Ad
curcumin 0.2%	96 Rao Coo. 01	2.0	49			post	Rf'	Phyto
fish oil 17% vs 20% lipid mix	97 Rao Hiros. 01	2.0	49	2.8		post	Rf'	lipid
retinamide 4-MPR 1mol/g	73 Zheng 97	2.0	49			both	Rf'	vit.Ad
Bifidobact. + lactulose	98 Challa 97	1.9	48		1.1	both	Rf'	Fibact
calcium 0.5% vs 0.1%	99 Thiagaraj. 98	1.9	48	1.9		post	Rf'	miner.
low polyamine diet	100 Duranton 97	1.9	47			post	Rw'	/NH2
dehydroepiandrosterone 0.5%	101 Pereira 91	1.9	47		1.1	init	Rs'	other
oxothiazolidine carboxylate ?%	101 Pereira 91	1.9	47		1.1	init	Rs'	other
Coptidis rhizoma extr 2%	102 Fukutake 98	1.9	47		1.0	init	Rf'	Phyto
zerumbone 500ppm	103 Tanaka 01	1.9	46	15.8	1.3	both	Rf'	Phyto
B-carotene 90ppm	104 Shivapu. 95	1.8	46	1.6		post	Rf	Phyto
starch resist.III 20% vs normal	105 Perrin 01	1.8	46		1.1	init	Rb'"	Fibact
squalene 1%	89 Rao New. 98	1.8	46	1.7		both	Rf'	lipid
vit.D 24R.25-diOH 10ppm	106 Taniyam. 00	1.8	45	1.7		post	Rf'	vit.Ad
Bifidobact. + Neosugar 5%	107 Koo 91	1.8	45		1.0	both	Mf"	Fibact
auraptene 500ppm	108 Tanaka 98	1.8	44		1.4	post	Rf'	Phyto
calcium carbonate 1.6%	109 Pereira 94	1.8	44	1.1		init	Rf'	miner.
capsanthin 0.2mg/d	110 Narisawa 00	1.8	44	1.8		post	Rf"	Phyto
indomethacin 2mg/kg	111 Charal. 96	1.8	44		1.0	both	Rs	NSAID
Aspirin 200ppm	58 Wargov. 95	1.8	43	2.7		post	Rf'	NSAID
lemon grass extract 5g/kg	112 Suaeyun 97	1.7	42	1.7	1.0	post	Rf'	Phyto
genistein 150ppm	99 Thiagaraj. 98	1.7	42	2.3		post	Rf'	Phyto
lutein 0.12mg/d /*MNU*	93 Narisawa 96	1.7	42	1.4		post	Rs"	Phyto
curcumin 0.2%	77 Rao Kaw. 99	1.7	42	1.6		both	Rf'	Phyto
geranyl EGMP 0,2%	113 Han 01	1.7	41	2.1	1.0	post	Rf'	other
sulindac 320ppm	109 Pereira 94	1.7	41		1.1	init	Rf'	NSAID
celecoxib 0.15%	114 Reddy R. 96	1.7	41	1.9		both	Rf'	NSAID
glucarate calcium 5%	109 Pereira 94	1.7	41	0.9		init	Rf'	Phyto
sinigrin 400ppm	115 Smith 98	1.7	41		0.9	post	Rw'	Phyto
acetoxychavicol acet. 100ppm	116 Tanaka 97	1.7	41	3.2	1.1	post	Rf'	Phyto
green tea (2% as drink)	117 Jia 01	1.7	41	2.0		both	Rw'	Phyto
butylhydroxyanisole 0.4%	118 Lam 91	1.7	40		1.1	init	Mf"	other
low fat 5% vs 20% lipid mix	97 Rao Hiros. 01	1.7	40	2.3		post	Rf'	lipid
mangiferin 0,1%	119 Yoshimi 01	1.7	40	2.1	1.1	both	Rf'	Phyto
garcinol 500ppm	120 Tanaka 00	1.7	40	2.8	1.1	init	Rf'	Phyto
calcium 0.3g/d in whole bread	121 Wargov. 01	1.7	40	2.0		post	Rf	miner.
chlorophillin 0.1% /*PhIP*	32 Guo 95	1.7	39	4.7	1.6	both	Rf'	Phyto
piroxicam 125ppm	109 Pereira 94	1.6	38		1.1	init	Rf'	NSAID
pectin 10%	122 Rao Ch. 98	1.6	38	2.7	1.1	both	Rf'	Fibact
wheat bran 10 vs 20%res.starch	123 Young 96	1.6	38			both	Rs	Fibact

Table 1. *(Continued)*

Agent /*Carcinogen* [a]	Ref. author, year.	Potency to Reduce ACF No. [b]	%Inhibition of ACF [c]	Potency on Large ACF [d]	Potency on ACF Size [e]	Pro-Tocol [f]	Ro-dent [g]	Class of Agent [h]
docosahexaenoic 0.7ml/d	124 Takahas. 97	1.6	38	2.0	1.1	init	Rf'	lipid
unrefined wheat diet /*IQ*	125 Yu 01	1.6	38	1.2	1.1	post	Rf'	Fibact
butyltiophene 100ppm	27 Wargov. 00	1.6	38		0.9	init	Rf'	other
geranyl EGMP 0.2%	126 Tsuda 99	1.6	37	2.0	1.1	post	Rf'	other
sulindac 10mg/kg	111 Charal. 96	1.6	37	1.6	0.9	both	Rs	NSAID
starch vs sucrose bolus	127 Luceri 96	1.6	36			init	Rf"	other
allylthiopyrazine 50mg/kg	128 Kim 01	1.6	36	1.6	1.0	post	Rf'	Phyto
bezafibrate 500ppm	129 Tanaka 01	1.6	36		1.1	both	Rf'	other
ceramide-Bglucur. 0.1% /mice	130 Schmelz 99	1.6	36		1.2	post	Mf"	other
docosahexaenoic+EPA 0.3%	131 Paulsen 98	1.6	36	1.8		init	Rf	lipid
sulindac 320ppm	114 Reddy 96	1.6	36	1.7		both	Rf'	NSAID
oleanolic 200ppm	132 Kawam. 95	1.6	36		1.0	init	Rf'	Phyto
PPITC 0.4%	118 Lam 91	1.5	35		1.0	init	Mf"	Phyto
nimesulide 200ppm	133 Takahas. 96	1.5	35		1.0	both	Rf'	NSAID
inulin 10%	134 Reddy 97	1.5	35	1.4		both	Rf'	Fibact
thiocyanate PEITC 2µmol/d	135 Chung 00	1.5	35	1.9		post	Rf'	Phyto
tea extract EGCG 0.12%	136 Steele B. 99	1.5	35			init	Rf'	Phyto
genistein 150ppm	109 Pereira 94	1.5	34		1.0	init	Rf'	Phyto
cork 5% /*IQ*	137 Ferguson 98	1.5	34	5.6	1.5	both	Rf'	Fibact
raspberries 2.5%	138 Harris 01	1.5	34	1.3		post	Rf'	Phyto
N-acetylcysteine 0.2%	101 Pereira 91	1.5	34		1.1	init	Rs'	other
vit.A 200UI	139 Maziere 98	1.5	33			post	Rs'	vit.Ad
phytic acid 2%+ green tea	140 Challa 97	1.5	33		1.1	both	Rf'	Phyto
cantaxantin 500ppm	141 Tanaka 95	1.5	33		1.0	post	Rf'	Phyto
Roselle 0.1%	142 Chewon. 99	1.5	33			both	Rf'	Phyto
sulforaphane 2µmol/d	135 Chung 00	1.5	33	1.7		post	Rf'	Phyto
limonene 0.5% in water	143 Kawam. 96	1.5	32	2.3	1.1	init	Rf'	Phyto
EP1 inhib. ono8713 159ppm	144 Watanab. 00	1.5	32		1.2	post	Mc'	NSAID
potato starch 67% vs mix	145 Thorup 95	1.5	32	5.2		post	Rw'	Fibact
lutein 500ppm	146 Kim 98	1.5	32		1.0	post	M6	Phyto
NOS inhibit. L-NAME 100ppm	147 Kawam. 00	1.5	32	1.6		both	Rf'	NSAID
Clostridium perfr. cult 1E9/ml	148 Arimochi 97	1.5	31		1.0		Rs'	Fibact
COX2 inhibitor NS-398 10ppm	149 Oshimi 97	1.4	31	2.3		post	Rf'	NSAID
phytic acid 1%	150 Jenab 98	1.4	31			post	Rf'	Phyto
calcium 1% vs 0.5%	151 Li Kram. 98	1.4	31	2.0		init	Rf'	miner.
Bifidobact. + FOS 2%	152 Gallaher 99	1.4	30		1.0	post	Rw'	Fibact
lovastatin 50+ sulindac 80ppm	153 Agarwal 99	1.4	28	1.4		both	Rf'	other
folate deficiency vs 0.8%	154 LeLeu 00	1.4	28	1.2		both	Rs'	other
white ginseng 1%	61 Li Wanib. 00	1.4	27	1.5		post	Rf'	Phyto
curcumin tetraHydro 0.5%	132 Kim 98	1.4	26		1.0	post	M6	Phyto
vitamin D3 10ppm	155 Salim 97	1.3	24	2.8		post	Rf'	vit.Ad
ursodeoxycholic acid 0.4%	156 Ikegami 98	1.3	23			both	Rf'	other
wheat bran 25% vs 5% cell.	156 Jenab 98	1.3	22		1.0	post	Rf'	Fibact
low fat 7% vs 22%	157 Moroto. 97	1.2	18	2.3	1.1	both	Rf'	lipid
veget.juice (lycopene) =drink	158 Arimochi 99	1.2	18	1.9	1.1	both	Rf'	Phyto

Table 1. *(Continued)*

Agent /*Carcinogen* [a]	Ref. author, year.	Potency to Reduce ACF No. [b]	%Inhibition of ACF [c]	Potency on Large ACF [d]	Potency on ACF Size [e]	Pro-Tocol [f]	Ro-dent [g]	Class of Agent [h]
flaxseed 5%	159 Jenab 96	1.2	16	1.9	1.1	both	Rs'	Phyto
phytate 2%	160 Pretlow 92	1.2	16	1.8		post	Rf'	Phyto
butyrate pellets 150mg/d	161 Caderni 98	1.2	15	1.6	1.0	post	Rf'	Fibact
selenomethionine 2ppm	162 Baines 00	1.2	14	2.2		post	Rf'	other
GOS 20%	163 Wijnands 01	1.1	11	1.3	1.1	post	Rf'	Fibact
lycopene 10ppm	164 Jain 99	1.1	7		1.0	both	Rf'	Phyto
peas 10%	165 Rijken 99	1.0	3	2.1	1.2	both	Rs'	Phyto

a: Doses are reported as percentage of diet (wt/wt), ppm (1,000 ppm = 0.1%), or mg/kg body wt. Unless otherwise noted, azoxymethane or 1,2-dimethylhydrazine was the carcinogen. Abbreviations are as follows: BHA, butylated hydroxyanisol; BseSG, benzyl selenocyanate glutathione conjugate; CAI, carboxyl amidoimidazole; CLA, conjugated linoleic acid; 2-CPR, 2-(carboxyphenyl)retinamide; DHEA, dehydroepiandrosterone; DHA, docosahexaenoic acid; DMABP, 3,2′-dimethyl-4-aminobiphenyl; EGMP, Ethylgeranyloxymethoxyphenyl-propenoate; EP1, prostaglandin E receptor subtype; EPA, eicosapentaenoic acid; FOS, fructooligosaccharide; GOS, glucooligosaccharide; 4-HPR, 4-(hydroxyphenyl)retinamide; IQ, 2-amino-3-methylimidazo[4-5-*f*]quinoline; L-NAME, *N*-nitroso-L-arginine methyl ester; MNU, methylnitrosourea; 4-MPR, 4-(methoxyphenyl)retinamide; MTD, maximum tolerated dose; NO, nitric oxide; NOS, inducible NO synthase; PBIT, *S,S* ′-1,4-phenylene-bis(1,2-ethanediyl)bisisothiourea; PEITC, phenethyl isothiocyanate; PEMC, phenylethyl-3-methylcaffeate; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; PPITC, phenylpropyl isothiocyanate; PSK, protein-bound polysaccharide PSK; RA, retinoic acid; TGF-β1, transforming growth factor-β1; TNBS, trinitrobenzenesulfonic acid.

b: A potency index was estimated for each agent by calculating ratio of mean value in control rats to mean value in treated rats. Thus potency tells magnitude reduction in number of ACF, number of large ACF, or ACF mean size due to the agent. For instance, in the study of Wargovich et al. (27), a mean number of 193 ACF were observed in control rats and 28 ACF in rats given sulindac sulfide: potency of sulindac sulfide to reduce ACF number was calculated as 193/28 = 6.89.
c: Percent inhibition afforded by agent is equal to 100 − 100/potency.
d: Most articles report ACF of ≥4 crypts as large ACF. Values missing in original article are not reported here.
e: ACF size measured as mean number of aberrant crypts per ACF.
f: Agent was given to animals during initiation with chemical carcinogen (init), after the end of initiation (post), or during both periods (both).

g: Rodent: species, strain, and gender; e.g., Rf′ = Fischer 344 male rats; ′, male; ″, female. Rats: Ra, ACI/N; Rb, BDIX; Rc, CD; Rd, Donryu; Rf, Fischer 344; Rl, LIO; Rr, Charles River; Rs, Sprague-Dawley; Rw, Wistar; R6, DB6. Mice: Mb, Balb/c; Mc, C57B/6J; Md, CD1; Mf, CF1; Mi, ICR; Ms, SW; M6, B6C3F1.

h: Nine classes of agents: /NH2, amine modulators and difluoromethylornithine (DFMO); Fibact, dietary fibers and probiotic bacteria; lipids; minerals; NSAID, nonsteroidal anti-inflammatory drug; PEG, polyethylene glycol; Phyto, phytochemicals and plants; Vit, vitamins A and D and retinoids; others.

Table 2. Ranking agents by chemopreventive potency to reduce the tumors in the colon of rats (or mice) after initiation with a chemical carcinogen.

Agent, dose / *Carcinogen* [a]	Ref., author, year	Potency to Reduce Tumor Incidence [b]	%Inihibition of Tumor Incidence [c]	Tum. Incid. control-treated [d]	%Inhibition of Cancer Incidence	Potency to Reduce Tum. Multiplicity	Pro-tocol [e]	Ro-dent [f]	Class of Agent [g]
celecoxib 0.15%	166 Kawamori 98	15.4	93	29/34 2/36	96	31.8	both	Rf'	NSAI
Bifidobact. longum 0.5% /IQ	167 Reddy Ri. 93	14.0	93	**7**/30 0/30		25.8	both	Rf'	fibact.
BB protease inh. 0.5% /mice	168 StClair 90	10.4	90	**7**/62 1/92	87	10.1	both	Md'	phyto.
DFMO 0.2%+pirox. 200ppm	169 Rao Toku. 91	9.0	89	27/36 3/36	88	16.0	both	Rf'	NSAI
PEG 8000 5%	28 Corpet 00	8.6	88	22/27 2/21	100	10.3	post	Rf'	PEG
MMTS 100ppm	170 Kawamori 95	7.9	87	17/30 2/28	100		post	Rf'	phyto.
BB protease inh. 0.5% /mice	171 Weed 85	7.3	86	**7**/46 0/24		11.5	both	Md'	phyto.
PEG 8000 5%	33 Parnaud 99	7.0	86	14/20 1/10	100	21.0	post	Rf'	PEG
folate 8ppm	172 Kim 96	7.0	86	**7**/10 1/10		11.0	both	Rs'	phyto.
piroxicam 200ppm	173 Li Kramer 99	6.5	85	% 100 15	63	3.3	post	Rf'	NSAI
pectin 15% vs cellulose 5%	174 Redd87 /w79	5.7	82	% 57 10			both	Rf'	fibact.
obacunone 500ppm	54 Tanaka Ma. 01	5.5	82	18/25 2/16	82	6.4	post	Rf'	phyto.
DFMO 0.1%+aspir. 0.06%	175 Li Schut 99	5.3	81	% 71 13.3	38	6.0	both	Rf'	NSAI
Mg(OH)2 500ppm	176 Mori 93	5.3	81	17/32 3/30	77	7.5	post	Rf'	miner.
copper 8ppm vs 0.2ppm	177 diSilvestro 92	5.0	80	**5**/11 1/11		3.2	both	Rs'	miner.

Table 2. *(Continued)*

Agent, dose / *Carcinogen* [a]	Ref., author, year	Potency to Reduce Tumor Incidence [b]	%Inihibition of Tumor Incidence [c]	Tum. Incid. control-treated [d]	%Inhibition of Cancer Incidence	Potency to Reduce Tum. Multiplicity	Pro-tocol [e]	Ro-dent [f]	Class of Agent [g]
glucarate calcium 0.1mol/kg	178 Dwivedi 89	5.0	80	**5**/18 1/18			post	Rf"	phyto.
tetracycline 10mg/d /meat	179 Goldin 81	4.8	79	15/31 3/30		4.8	both	Rf'	fibact.
butylhydroxyanisol .6% /mice	180 Reddy M. 83	4.8	79	14/57 2/39		9.4	init	Mf"	other
hesperidin 0.1%	63 Tanaka Ma. 97	4.7	79	12/17 3/20	79	5.9	post	Rf'	phyto.
DFMO 0.2%	169 Rao Toku. 91	4.5	78	% 75 16.6	77	5.8	both	Rf'	/NH2
germfree vs normal flora	181 Reddy Na. 75	4.5	78	14/15 5/24	91	10.5	both	Rf'	fibact.
celecoxib 0.15%	182 Reddy Hi. 00	4.5	78	% 76 17	77	6.1	both	Rf'	NSAI
quercetin 2% /mice	183 Deschner 91	4.3	76	8/32 2/34		6.4	both	Mf	phyto.
beef vs milk protein /mice	184 Nutter 83	4.2	76	61/91 15/95		6.3	both	Mb'	other
wheat bran +caloric.rest.-10%	185 Kritchevs. 97	4.2	76	16/23 4/24			post	Rf'	fibact.
soy protein 20% vs casein	186 Hakkak 01	4.1	76	21/42 5/41	69		both	Rs	other
aspirin 60mg/kg/d	187 Davis 94	4.0	75	8/8 2/8		8.3	both	Rw'	NSAI
olive vs corn oil 23.5%	188 Reddy M. 84	3.5	72	% 46 13			post	Rf'	lipid
acetoxychavicol 500ppm	189 Tanaka K. 97	3.5	72	12/17 4/20	93	2.8	post	Rf'	phyto.
piroxicam 400ppm	169 Rao Toku. 91	3.4	70	% 75 22.2	70	3.4	both	Rf'	NSAI
caloric restriction -30%	185 Kritchevs. 97	3.3	70	16/23 5/24			post	Rf'	other
low risk vs high risk diet	190 Rao Goett. 88	3.3	70	% 42 12.5	86		both	Rf"	other
vit.D3-6Fl RO24 2.5nmol/kg	191 Wali 95	3.3	70	10/20 3/20		3.3	init	Rf'	vit.Ad
phytate 2% in water	160 Pretlow 92	3.3	70	10/12 3/12	70	2.7	post	Rf'	phyto.
sulindac sulfone 0.12%	192 Reddy Ka. 99	3.3	69	% 85 26	68	6.0	both	Rf'	NSAI
purple corn color 5% /PhIP	193 Hagirawa 01	3.2	68	19/20 6/20	91	9.0	both	Rf'	phyto.
yugao 10% /mice	194 Furukawa 95	3.0	67	9/18 3/18	67	6.0	both	Mi	fibact.
sulindac sulfone 0.2%	195 Piazza 97	3.0	66	% 80 27	81	4.7	post	Rf'	NSAI
aspirin 10ppm	196 Craven 92	2.9	66	% 50 17	66	2.9	init	Rs'	NSAI
protocatechuic acid 0.1%	197 Tanaka K. 93	2.9	65	15/20 6/23	71	4.3	post	Rf'	phyto.
ursodeoxycholic 0.4%	198 Earnest 94	2.9	65	10/20 4/23	100	2.9	both	Rf'	other
cellulose 20% vs 3%	199 Madar 96	2.8	64	23/25 6/18	86	2.6	both	Rs'	fibact.
pravastatin 10ppm /mice	200 Narisawa 96	2.8	64	16/29 6/30		1.3	both	Mi	other
piroxicam 400 ppm	201 Reddy T. 92	2.8	64	% 61 22.2	67	2.7	both	Rf'	NSAI
fish oil 23.5% vs corn oil	202 Reddy M. 86	2.8	64	22/24 8/24	73	5.2	post	Rf'	lipid
psyllium 15% vs cellulose 5%	203 Wilpart 87	2.8	64	11/32 4/32		1.5	both	Rw'	fibact.
Lactobac. acidoph. 1%	204 McIntosh 99	2.7	63	% 40 15		3.3	both	Rs'	fibact.
rice germ 2.5%	74 Kawabata 99	2.6	62	15/20 4/14	62	1.6	init	Rf'	phyto.
tomato juice (lycop) */MNU*	205 Narisawa 98	2.6	62	13/24 5/24	62	2.0	both	Rf"	phyto.
wheat bran 10%+wb.oil 2%	206 Reddy H. 00	2.6	61	% 77 30	57	3.2	both	Rf'	fibact.
KYN-54 200ppm	207 Kawamori 95	2.6	61	11/30 4/28	77	1.4	post	Rf'	vit.Ad
nerolidol 0.5%	208 Wattenb. 91	2.5	60	% 82 33		2.1	post	Rf'	other
putrescine inj. 150µmol/kg	209 Tatsuta 91	2.4	58	16/20 6/18		2.5	both	Rw'	/NH2
allylcysteine 400ppm /mice	210 Sumiyoshi 90	2.4	58	19/30 8/30	83	3.6	both	Mc	phyto.
glucarate KHd- 0.14mol/kg	211 Yoshimi 00	2.3	57	15/26 6/24		2.6	post	Rf'	phyto.
E-aminocaproic 1g/l /mice	212 Corasanti 82	2.3	56	17/17 7/16		8.0	both	Mi	other
canthaxantin 500ppm	141 Tanaka K. 95	2.3	56	17/30 7/28	67	3.3	post	Rf'	phyto.
menadione 9mg/kg/d /mice	213 Bi 93	2.3	56	9/13 4/13		7.0	both	Mi	other
cellulose 25% vs no fiber	214 Madar 93	2.3	56	18/20 4/10		4.4	both	Rs'	fibact.
pectin apple 20% vs cell.5%	215 Ohkami 95	2.2	55	% 83 37	65	3.5	both	Rd'	fibact.

Table 2. *(Continued)*

Agent, dose / *Carcinogen* [a]	Ref., author, year	Potency to Reduce Tumor Incidence [b]	%Inihibition of Tumor Incidence [c]	Tum. Incid. control-treated [d]	%Inhibition of Cancer Incidence	Potency to Reduce Tum. Multiplicity	Pro-tocol [e]	Ro-dent [f]	Class of Agent [g]
sulindac 320ppm	216 Rao Riv. 95	2.2	55	NR	55	3.0	both	Rf'	NSAI
sphingomyelin 500ppm/mice	217 Dillehay 94	2.2	54	**7**/15 3/14		1.5	post	Mf	lipid
selenocyanate pXSC 40ppm	218 Reddy Ri. 92	2.2	54	% 80 37		3.3	post	Rf'	other
calcium 0.32% vs 0.04%	219 Wargovic. 90	2.1	53	% 68 32		1.8	both	Rf"	miner.
selenocyanate benzyl 50ppm	220 Nayini 91	2.1	53	%100 47.2	52	3.0	init	Rf'	other
selenium 4ppm (NaSe)	220 Nayini 91	2.1	53	%100 47.3	48	2.2	post	Rf'	other
p53 vaccination	221 Zusman 98	2.1	52	42/45 8/18	62	11.6	both	Rs	other
beans dry 59%	222 Hughes 97	2.1	52	10/20 5/21	47	6.5	post	Rf'	phyto.
phytate 1%	223 Ullah 90	2.1	52	17/29 14/50		2.3	both	Rf'	phyto.
perilla oil 12% */MNU*	224 Narisawa 94	2.1	52	20/30 8/25		2.5	both	Rf"	lipid
paprika juice (capsant.) */MNU*	110 Narisawa 00	2.1	52	% 83 40		2.3	both	Rf"	phyto.
eicosapentaenoic 4.7%	225 Minoura 88	2.1	52	20/29 10/30		4.1	both	Rd'	lipid
amiloride 7.5ppm	226 Tatsuta 95	2.0	51	15/19 7/18		1.9	both	Rw'	other
green tea polyphenols 0.1%	227 Yamane 91	2.0	51	17/22 8/21		2.4	post	Rf'	phyto.
nimesulide 400ppm /mice	228 Fukutake 98	2.0	50	NR	50	5.1	both	Mi'	NSAI
auraptene 500ppm	108 Tanaka K. 98	2.0	49	16/27 6/20		2.0	post	Rf'	phyto.
hesperidin 7mg/d mandarin	229 Tanaka K. 00	2.0	49	20/29 7/20	78	2.1	post	Rf'	phyto.
selenocyanate pXSC 20ppm	230 Reddy Ri. 97	2.0	49	% 53 27	-70	2.9	post	Rf'	other
Lactobac. acidoph. 1E10	231 Goldin 80	1.9	48	% 77 40	48		both	Rf'	fibact.
ursodeoxycholic 0.08%*/MNU*	232 Narisawa 98	1.9	47	17/25 9/25		2.5	post	Rf"	other
wheat bran 12% vs oat bran	233 Zoran 97	1.9	47	17/33 9/33			both	Rs'	fibact.
whey protein 20% vs casein	234 Hakkak 01	1.9	47	18/32 14/47	32		both	Rs	other
PEMC caffeate 750ppm	235 Rao Des. 95	1.9	47	% 81 43	66	2.0	both	Rf'	phyto.
anethole trithione 200ppm	236 Reddy Ra. 93	1.9	46	% 78 42	46	2.6	both	Rf'	phyto.
ibuprofen 400 ppm	201 Reddy T. 92	1.8	46	% 61 33.3	43	2.0	both	Rf'	NSAI
low fat 5% vs 18%lard */MNG*	237 Sinkeldam 90	1.8	45	% 73 40	0	2.1	both	Rw'	lipid
calcium 2% vs 0.5%	238 Karkare 91	1.8	45	21/28 7/17	-229	1.8	post	Rf'	miner.
whey protein 21% vs meat	239 McIntosh 94	1.8	45	%53.7 29.5			both	Rs'	other
mangiferin 200ppm	119 Yoshimi 01	1.8	44	12/22 8/26		1.2	post	Rf'	phyto.
selenium 2.5ppm (NaSe)	240 Reddy Su. 88	1.8	43	21/27 12/27	90	2.6	post	Rf'	other
carbon fiber activated 1g/kg	241 Anisimov 99	1.7	42	20/21 11/20		2.4	both	Rl"	other
wine extract (red) 50mg/kg	242 Caderni 00	1.7	42	19/22 11/22	-31	1.6	post	Rf'	phyto.
wheat bran 15% vs 5%cell.	174 Redd87 /w79	1.7	42	% 57 33			both	Rf	fibact.
curcumin 0.2%	243 Rao Riv. 95	1.7	42	% 81 47	47	2.3	both	Rf'	phyto.
caloric restriction -30%	244 Holt 96	1.7	42	% 88.9 51.8		2.2	both	Rf'	other
low fat 5% vs 20% corn oil	244 Holt 96	1.7	42	% 88.9 51.8		2.1	both	Rf'	lipid
oltipraz 200ppm	245 Rao Riv. 93	1.7	40	% 78 47	40	2.4	init	Rf'	phyto.
aspirin 400ppm	246 Reddy Ra. 93	1.7	40	% 78 47	84	2.3	post	Rf'	NSAI
vit.D 0.1ppm+ calcium 1.5%	247 Beaty 93	1.7	40	12/30 7/29	44		post	Rf'	vit.Ad
B-sitosterol 0.2% */MNU*	248 Raicht 80	1.6	39	% 100 61	60			R	lipid
fish oil 16% vs soy 4% /mice	249 Lindner 91	1.6	39	% 90 55	63	2.1	both	Ms	lipid
selenocyanate benzyl 25ppm	250 Reddy Su. 87	1.6	38	21/27 13/27	70	2.0	init	Rf'	other
vit.D 24R25 5ppm	106 Taniyama 00	1.6	38	% 92 57		2.8	post	Rf'	vit.Ad
voluntary exercise <2 miles/d	251 Reddy Su. 88	1.6	38	% 66 41	64	2.8	post	Rf'	other
low meat 25% vs 60%	252 Reddy Na. 76	1.6	38	16/28 10/28		2.0	both	Rf'	other

Table 2. *(Continued)*

Agent, dose / *Carcinogen* [a]	Ref., author, year	Potency to Reduce Tumor Incidence [b]	%Inihibition of Tumor Incidence [c]	Tum. Incid. control-treated [d]	%Inhibition of Cancer Incidence	Potency to Reduce Tum. Multiplicity	Pro-tocol [e]	Ro-dent [f]	Class of Agent [g]
selenocyanate pXSSG 56ppm	253 Rao Wang 01	1.6	37	% 83 52	0	1.5	post	Rf'	other
low fat 5% vs 20% lipid mix.	97 Rao Hirose 01	1.6	37	% 100 63	67	3.9	post	Rf'	lipid
caloric restriction -30%	254 Kumar 90	1.6	37	% 85 52	42	2.1	post	Rf'	other
curcumin 4% /mice	255 Huang 94	1.6	37	% 93 59	63	2.6	both	Mf	phyto.
maltitol 5%	256 Tsukamur. 98	1.6	37	15/20 10/21		2.1	both	Rf'	fibact.
wheat bran vs resist.starch	123 Young 96	1.6	36	% 88 56		1.8	both	Rs	fibact.
mofarotene 100ppm	257 Tanaka 96	1.5	35	17/22 9/18	76	1.8	post	Rf'	vit.Ad
DEHA 0.6% /mice	258 Nyce 84	1.5	35	26/26 17/26	36	5.1	both	Mb"	other
aceglatone 2%	72 Yoshimi 01	1.5	34	% 50 33			init	Rf'	phyto.
omeprazole 40µM/kg	259 Penman 93	1.5	34	19/20 12/19		3.0	both	Rs"	NSAI
calcium lactacte 3g/l	260 VinasSall. 98	1.5	33	28/29 18/28		1.7	both	Rs	miner.
melatonin 20mg/l water	261 Anisimov 97	1.5	33	21/21 14/21		2.5	both	Rl	other
flavonoid morin 500ppm	262 Tanaka 99	1.5	33	9/12 7/14	62	2.0	post	Rf'	phyto.
lactoferrin bovin 2%	263 Sekine 97	1.5	32	31/40 21/40	74	1.7	post	Rf'	other
fish oil 18% vs corn oil	264 Reddy Su. 88	1.5	32	25/27 17/27	55	1.8	post	Rf'	lipid
tea extract (black) 50mg/kg	242 Caderni 00	1.5	32	19/22 13/22	0	1.7	post	Rf'	phyto.
veg.&fruits 20% */MNG*	265 Rijnkels 97	1.5	32	% 73 50	70	2.1	both	Rw'	phyto.
fish oil 17% vs lipid mix.	97 Rao Hirose 01	1.4	31	% 100 69	50	3.1	post	Rf'	lipid
Bifidobact. longum 2%	266 Singh 97	1.4	30	23/30 16/30		2.2	both	Rf'	fibact.
BB protease inhib. 0.1%/mice	267 Billings 90	1.4	30	13/19 11/23	45	1.4	both	Md	phyto.
citrus pulp 15%	174 Reddy 87 /81	1.4	30	% 90 63	38	1.9	both	Rf'	fibact.
treadmill exercise 5h/d	268 Thorling 94	1.4	30	31/31 21/30	100	1.6	post	Rf'	other
vit. D3 -OH 0.04µg*/MNU*	269 Kawaura 90	1.4	29	17/25 12/25	28	1.4	both	Rf	vit.Ad
pectin 10% vs no fiber	270 Heitman 92	1.4	29	22/30 19/30		1.5	post	Rs'	fibact.
cryptoxanthin 25ppm */MNU*	271 Narisawa 99	1.4	29	24/25 17/25		1.2	both	Rf"	phyto.
Lactobac. rhamnos. GG 2E10	272 Goldin 96	1.4	29	% 100 71		2.1	init		fibact.
perillyl alcol 0.2%	273 Reddy W. 97	1.4	28	NR	29	1.2	both	Rf'	phyto.
B-carotene 50ppm	274 Yamamot. 94	1.4	28	NR	28	1.3	both	Rs'	phyto.
Lactobac. bulg. milk2.5g/d	275 Balanski 99	1.4	27	% 96.6 70.8		1.7	both	R6"	fibact.
plumbagin 200ppm	276 Sugie 98	1.3	26	13/28 10/29	3	1.9	init	Rf'	phyto.
raspberries 10%	138 Harris 01	1.3	25	% 67 50		3.5	post	Rf'	phyto.
wheat aleurone flour 33%	277 McIntosh 00	1.3	25	% 80 60		1.6	both	Rs'	fibact.
curcumin 0.6%	278 Kawamori 99	1.3	25	% 85 64	29	2.3	post	Rf'	phyto.
wheat bran 24% */MNNG*	237 Sinkeldam 90	1.3	25	% 73 55	0	1.9	both	Rw'	fibact.
N-acetylcystein .2%/dss mice	279 Seril 01	1.3	23	23/26 17/25		1.4	both	Mc	other
orange juice as drink	280 Miyagi 00	1.3	22	% 73 57		1.2	post	Rf'	phyto.
fish oil 15% vs corn oil 15%	281 Chang 97	1.3	20	NR	20		both	Rs'	lipid
sphingomyelin 250ppm /mice	47 Schmelz 96	1.3	20	% 24.5 19.6	40	1.0	post	Mf	lipid
folate deficency vs 8mg/kg	282 LeLeu 00	1.2	19	% 79 64	77	1.8	both	Rs'	other
GOS 20%	163 Wijnands 01	1.2	17	% 83.6 69.2	10	1.1	both	Rf'	fibact.
pectin 6% vs cellulose 6%	281 Chang 97	1.2	16	NR	17		both	Rs'	fibact.
calcium 2% /cholic acid diet	283 Pence 95	1.2	15	% 85 72	-12	1.2	post	Rf'	miner.
benzyl thiocyanate 400ppm	284 Sugie 94	1.2	13	15/18 13/18	-18	0.7	post	Ra"	phyto.
retinamide 4-HPR 2mmol/kg	73 Zheng 97	1.2	13	% 96.7 84	64	2.3	both	Rf'	vit.Ad
MMTS 80ppm	285 Reddy Ka. 99	1.1	12	% 85 75	59	1.4	post	Rf'	phyto.

Table 2. *(Continued)*

Agent, dose / *Carcinogen* [a]	Ref., author, year	Potency to Reduce Tumor Incidence [b]	%Inihibition of Tumor Incidence [c]	Tum. Incid. control-treated [d]	%Inhibition of Cancer Incidence	Potency to Reduce Tum. Multiplicity	Pro-tocol [e]	Ro-dent [f]	Class of Agent [g]
docosahexaenoic 1ml/d	113 Takahashi 97	1.0	5	52/54 45/49	5	1.5	both	Rf'	lipid
veg.&fruits 20%	286 Alink 93	1.0	4	% 84 81	5	1.9	both	Rw'	phyto.
vitamin D3 2UI/g stress diet	287 Mokady 00	1.0	0	% 100 100	0	6.0	both	Rr'	vit.Ad
tannin red ald. 10mg/kg mice	62 GaliMuht. 01	1.0	0	% 100 100	0	2.8	init	Mb	phyto.
TGF-B1 2ng/d	48 Mikhailow 98	1.0	0	% 100 100		2.7	both	Rc	other
wheatbran microfib.20%mice	288 Takahashi 99	1.0	0	18/19 18/19	0	2.6	both	Mf	fibact.
vit. D3 1.25diOH 5x0.4µg	289 Belleli 92	1.0	0	**5**/5 7/7	0	2.1	init	Rr'	vit.Ad
low calcium 0.1% vs 1%	290 Bull 87	1.0	0	% 100 100		1.7	both	Rs'	miner.
Na2SO4 0.25% low fecal pH	291 Samelson 85	1.0	0	% 100 100		1.5	both	Rs'	fibact.
butyrate pellets 1.5%	292 Caderni 01	0.9	-14	% 79 90		0.8	post	Rf'	fibact.

a: Abbreviations are as follows: BBI, Bowman-Birk protease inhibitor; MMTS, *S*-methyl methane thiosulfonate; RO24-6Fl-Vit D_3, 1⟨,25$(OH)_2$-16-ene-23-yne-26,27-hexafluorocholecalciferol; KYN-54, 5-hydroxy-4-(2-phenyl-(*E*)-ethenyl)-2(5*H*)-furanone; pXSC, 1,4-phenylenebis(methylene)selenocyanate. See Table 1 Footnote a for other abbreviations and further information.

b: Potency of each agent was estimated by ratio of value in control rats to value in treated rats. We used tumor data confirmed by histology, when available. For instance, in the study of Corpet et al. (28), incidence of tumors (confirmed by histology) was 22 of 27 in control group and 2 of 21 in rats given PEG: potency of PEG to reduce tumor incidence was calculated as (22/27)/(2/21) = 8.55. Potency is inverse of relative risk (e.g., a potency of 8.55 corresponds to a relative risk of 0.12).

c: Percent inhibition afforded by the agent is equal to (100 □ 100/potency).

d: Values represent number of tumor-bearing rats per total number of rats or %tumor incidence in control and treated groups. Potency based on small numbers (<8) of tumor-bearing rats is not accurate (data in boldface). When no tumor was seen in control group, potency calculation was arbitrarily based on 0.5 tumors in the group. NR, not reported.

e: See Table 1 Footnote f.
f: See Table 1 Footnote g.
g: See Table 1 Footnote h.

Added to Author's Version, May 31, 2008

- A shorcut to the Chemoprevention Database website, updated each year:
http://www.inra.fr/reseau-nacre/sci-memb/corpet/indexan.html is
http://corpet.net/min and a mirror site is found at
http://corpet.free.fr/
- A similar systematic review on chemoprevention in the Min mouse model has been published in 2003 in CEBP:
Corpet DE, Pierre F. Point: From animal models to prevention of colon cancer. Systematic review of chemoprevention in min mice and choice of the model system. Cancer Epidemiol Biomarkers Prev. 2003, 12:391-400.
- A comparison of chemoprevention results obtaines in all rodent models with human clinical trial results has been published in EJC in 2005:
Corpet DE, Pierre F. How good are rodent models of carcinogenesis in predicting efficacy in humans? A systematic review and meta-analysis of colon chemoprevention in rats, mice and men. Eur J Cancer. 2005, 41:1911-22.