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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.

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

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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.

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 from 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 $100 - 100/\text{potency}$ (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 endpoints 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), chlorophyllin, 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 gluconate, were based on only 7 tumor-bearing rats or mice in their respective control group (see table 2, column 5).

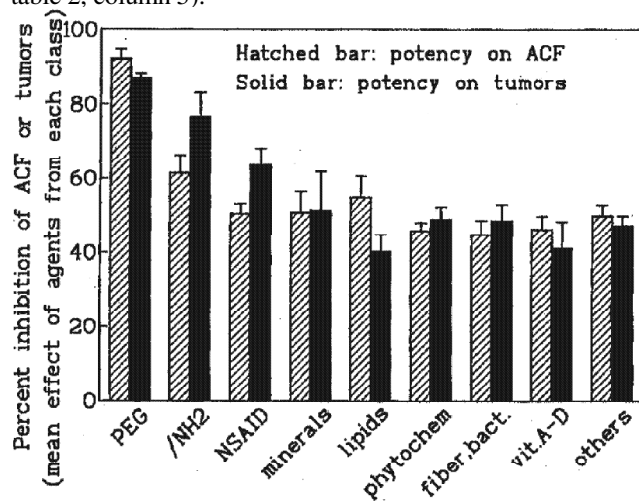


Figure 1. Mean potency of all chemopreventive agents in each class to reduce number of aberrant crypt foci (ACF) and tumor incidence in colon of rats. Nine classes are as follows: polyethylene glycol (PEG), difluoromethylornithine and amine modulators (/NH₂), nonsteroidal anti-inflammatory drugs (NSAID), 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 ursodeoxycholic, 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.

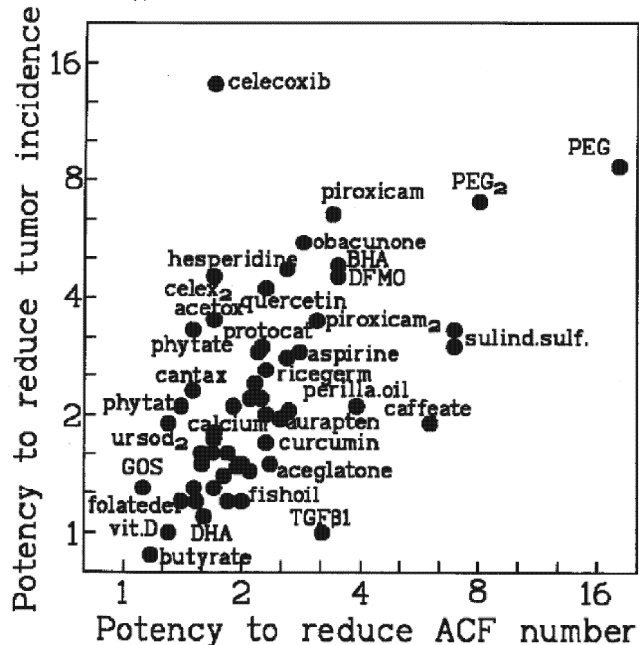


Figure 2. Correlation between potency of each agent to reduce number of ACF and to reduce incidence of tumors in colon of rats. Data from Tables 1 and 2 are shown on logarithmic scales. Points between 1.5 and 3 were too tight to be labeled. GOS, glucooigosaccharide; TGF- β 1, transforming growth factor- 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 ^m | | PEG |
| PEG 8000 5% /MNU | 28 Corpet 00 | 56.0 | 98 | 58.0 | 2.0 | post Rf ^f | | PEG |
| PEG 8000 5% | 30 Corpet 99 | 17.8 | 94 | 104.0 | 2.3 | post Rf ^m | | PEG |
| PEG 8000 5% | 29 Parnaud 01 | 14.0 | 93 | 14.0 | 1.1 | post Rf ^m | | PEG |
| perilla oil 12%+ B-carotene | 31 Komaki 96 | 11.4 | 91 | | 1.2 | init Rf ^f | | lipid |
| Indole3carbinol 0.1% /PhIP | 32 Guo 95 | 11.0 | 91 | 14.0 | 2.0 | init Rf ^f | | Phyto |
| PEG 8000 5% | 33 Parnaud 99 | 7.9 | 87 | 30.0 | 1.3 | post Rf ^m | | 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 ^f | | NSAID |
| caffeate PEMC 500ppm | 35 Rao Des. 93 | 5.6 | 82 | 21.0 | 1.0 | both Rf ^f | | Phyto |
| PEG 8000 5% | 36 Naigam. 00 | 5.5 | 82 | 36.0 | 1.4 | post Rf ^f | | PEG |
| grape proanthocyanidins 1% | 37 Singletary 01 | 4.3 | 77 | 4.6 | | both Rs ^m | | Phyto |
| trogglitazone 30mg/kg | 38 Kohno 01 | 4.2 | 76 | 5.4 | 1.4 | init Rf ^f | | other |
| linoleic CLA 0.5% /IQ | 39 Liew 95 | 3.9 | 74 | | 0.9 | init Rf ^f | | lipid |
| cooking salt 4.4% | 40 Masaoka 00 | 3.9 | 74 | | 1.0 | init Rf ^f | | miner. |
| perilla oil 12% vs olive oil | 41 Onogi 96 | 3.9 | 74 | | 1.1 | init Rf ^f | | lipid |
| <i>Bifidobact.1.7%</i> + inuline 5% | 42 Rowland 98 | 3.7 | 73 | 2.3 | | post Rs | | Fibact |
| butylhydroxyanisole 0.56% | 43 Wargov. 92 | 3.5 | 71 | | | init Rf ^f | | other |
| DFMO 0.4% | 43 Wargov. 92 | 3.5 | 71 | | | init Rf ^f | | /NH2 |
| DFMO 0.4% | 44 Wargov. 96 | 3.5 | 71 | | | init Rf ^f | | /NH2 |
| piroxicam 400ppm | 27 Wargov. 00 | 3.4 | 70 | | | post Rf ^f | | NSAID |
| sphingomyelin diOH 0.1%/mice | 45 Schmelz 97 | 3.3 | 70 | | 1.2 | post Mf ^m | | other |
| sanshishi 2% | 46 Fukutake 00 | 3.3 | 70 | | 1.5 | both Rf ^f | | Phyto |
| sphingomyelin 0.1% /mice | 47 Schmelz 96 | 3.3 | 69 | | 1.5 | post Mf ^m | | lipid |
| rutin 3% | 27 Wargov. 00 | 3.2 | 69 | | | post Rf ^f | | 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 ^f | | NSAID |
| starch vs sucrose-dextrin diet | 49 Poulsen 01 | 3.1 | 67 | 11.5 | | both Rf ^f | | other |
| retinoic acid allTrans 190ppm | 27 Wargov. 00 | 3.0 | 67 | 3.4 | | post Rf ^f | | 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 ^m | | other |
| piroxicam 125ppm 12to24wks | 52 Morishita 97 | 2.9 | 65 | 3.0 | | post Rf ^f | | NSAID |
| docosahexaenoic 0.5ml/d | 53 Takahashi 93 | 2.9 | 65 | | 1.2 | both Rf ^f | | lipid |
| obacunone 200ppm | 54 Tanaka 01 | 2.9 | 65 | | 1.1 | init Rf ^f | | Phyto |
| DFMO 0.4% | 55 Paulsen 97 | 2.9 | 65 | 6.2 | | both Rf ^f | | /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 ^f | | Fibact |
| piroxicam 200ppm | 58 Wargov. 95 | 2.8 | 64 | 8.0 | | post Rf ^f | | NSAID |
| docosahexaenoic 0.7ml/d/PhiP | 59 Takahashi 97 | 2.8 | 64 | 3.7 | 1.1 | init Rf ^f | | lipid |
| Taurine 1.2ppm | 27 Wargov. 00 | 2.7 | 64 | | | init Rf ^f | | other |
| beet fiber 10% /gamma ray | 60 Nagai 00 | 2.7 | 64 | | 0.7 | init Rw' | | Fibact |
| glycyrrhetic acid 0.5% | 41 Wargov. 96 | 2.7 | 63 | | | init Rf ^f | | Phyto |
| red ginseng 1% | 61 Li Wanib. 00 | 2.7 | 63 | 2.1 | | init Rf ^f | | 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-ident ^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 |
| <i>Bifidobacterium</i> 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 |
| <i>Bifidobact.longum</i> 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 | %Inhibiti on 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 Co. 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 |
| <i>Bifidobact.</i> + 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 2% | 101 Pereira 91 | 1.9 | 47 | | 1.1 | | init Rs' | other |
| <i>Coptidis rhizoma</i> 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 |
| <i>Bifidobact.</i> + 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. |
| chlorophyllin 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 | %Inhibiti on of ACF ^c | Potency on Large on 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 |
| <i>Clostridium perfr.</i> 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. |
| <i>Bifidobact.</i> + 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-ethanediy)bis(iso)thiourea; 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- β 1, transforming growth factor- β 1; 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 | %Inhibition 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 |
| <i>Bifidobact. longum</i> 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 | %Inhibition 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 ⁿ | phyto. |
| tetracycline 10mg/d /meat | 179 Goldin 81 | 4.8 | 79 | 15/31 3/30 | | 4.8 | | both Rf ^f | fibact. |
| butylhydroxyanisol .6% /mice | 180 Reddy M. 83 | 4.8 | 79 | 14/57 2/39 | | 9.4 | | init Mf ⁿ | other |
| hesperidin 0.1% | 63 Tanaka Ma. 97 | 4.7 | 79 | 12/17 3/20 | 79 | 5.9 | | post Rf ^f | phyto. |
| DFMO 0.2% | 169 Rao Toku. 91 | 4.5 | 78 | % 75 16.6 | 77 | 5.8 | | both Rf ^f | /NH2 |
| germfree vs normal flora | 181 Reddy Na. 75 | 4.5 | 78 | 14/15 5/24 | 91 | 10.5 | | both Rf ^f | fibact. |
| celecoxib 0.15% | 182 Reddy Hi. 00 | 4.5 | 78 | % 76 17 | 77 | 6.1 | | both Rf ^f | 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 ^f | other |
| wheat bran +caloric.rest.-10% | 185 Kritchevs. 97 | 4.2 | 76 | 16/23 4/24 | | | | post Rf ^f | 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 ^f | NSAI |
| olive vs corn oil 23.5% | 188 Reddy M. 84 | 3.5 | 72 | % 46 13 | | | | post Rf ^f | lipid |
| acetoxychavicol 500ppm | 189 Tanaka K. 97 | 3.5 | 72 | 12/17 4/20 | 93 | 2.8 | | post Rf ^f | phyto. |
| piroxicam 400ppm | 169 Rao Toku. 91 | 3.4 | 70 | % 75 22.2 | 70 | 3.4 | | both Rf ^f | NSAI |
| caloric restriction -30% | 185 Kritchevs. 97 | 3.3 | 70 | 16/23 5/24 | | | | post Rf ^f | other |
| low risk vs high risk diet | 190 Rao Goett. 88 | 3.3 | 70 | % 42 12.5 | 86 | | | both Rf ⁿ | other |
| vit.D3-6Fl RO24 2.5nmol/kg | 191 Wali 95 | 3.3 | 70 | 10/20 3/20 | | 3.3 | | init Rf ^f | vit.Ad |
| phytate 2% in water | 160 Pretlow 92 | 3.3 | 70 | 10/12 3/12 | 70 | 2.7 | | post Rf ^f | phyto. |
| sulindac sulfone 0.12% | 192 Reddy Ka. 99 | 3.3 | 69 | % 85 26 | 68 | 6.0 | | both Rf ^f | NSAI |
| purple corn color 5% /PhIP | 193 Hagirawa 01 | 3.2 | 68 | 19/20 6/20 | 91 | 9.0 | | both Rf ^f | 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 ^f | NSAI |
| aspirin 10ppm | 196 Craven 92 | 2.9 | 66 | % 50 17 | 66 | 2.9 | | init Rs ^f | NSAI |
| protocatechuic acid 0.1% | 197 Tanaka K. 93 | 2.9 | 65 | 15/20 6/23 | 71 | 4.3 | | post Rf ^f | phyto. |
| ursodeoxycholic 0.4% | 198 Earnest 94 | 2.9 | 65 | 10/20 4/23 | 100 | 2.9 | | both Rf ^f | other |
| cellulose 20% vs 3% | 199 Madar 96 | 2.8 | 64 | 23/25 6/18 | 86 | 2.6 | | both Rs ^f | 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 ^f | NSAI |
| fish oil 23.5% vs corn oil | 202 Reddy M. 86 | 2.8 | 64 | 22/24 8/24 | 73 | 5.2 | | post Rf ^f | lipid |
| psyllium 15% vs cellulose 5% | 203 Wilpart 87 | 2.8 | 64 | 11/32 4/32 | | 1.5 | | both Rw ^f | fibact. |
| <i>Lactobac. acidoph.</i> 1% | 204 McIntosh 99 | 2.7 | 63 | % 40 15 | | 3.3 | | both Rs ^f | fibact. |
| rice germ 2.5% | 74 Kawabata 99 | 2.6 | 62 | 15/20 4/14 | 62 | 1.6 | | init Rf ^f | phyto. |
| tomato juice (lycop) /MNU | 205 Narisawa 98 | 2.6 | 62 | 13/24 5/24 | 62 | 2.0 | | both Rf ⁿ | phyto. |
| wheat bran 10%+wb.oil 2% | 206 Reddy H. 00 | 2.6 | 61 | % 77 30 | 57 | 3.2 | | both Rf ^f | fibact. |
| KYN-54 200ppm | 207 Kawamori 95 | 2.6 | 61 | 11/30 4/28 | 77 | 1.4 | | post Rf ^f | vit.Ad |
| nerolidol 0.5% | 208 Wattenb. 91 | 2.5 | 60 | % 82 33 | | 2.1 | | post Rf ^f | other |
| putrescine inj. 150µmol/kg | 209 Tatsuta 91 | 2.4 | 58 | 16/20 6/18 | | 2.5 | | both Rw ^f | /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 ^f | 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 ^f | 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 ^f | fibact. |
| pectin apple 20% vs cell.5% | 215 Ohkami 95 | 2.2 | 55 | % 83 37 | 65 | 3.5 | | both Rd ^f | fibact. |

Table 2. (Continued)

| Agent, dose / Carcinogen ^a | Ref., author, year | Potency to Reduce Tumor Incidence ^b | %Inhibition 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 | |
| <i>Lactobac. acidoph.</i> 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 caffeine 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 Rf'' | 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 | %Inhibition 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 | RI | 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 |
| <i>Bifidobact. longum</i> 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. |
| <i>Lactobac. rhamnos.</i> 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. |
| <i>Lactobac. bulg.</i> 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 deficiency 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 | %Inhibition of Tumor Incidence ^c | Tum. Incid. control-treated ^d | %Inhibition of Cancer Incidence | Potency to Reduce Tum. Multiplicity | Pro-tocol ^e | Ro-dent ^f of Agent ^g | Class |
|---------------------------------------|--------------------|--|---|--|---------------------------------|-------------------------------------|------------------------|--|-------|
| 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 microfibr.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 Cademi 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; RO24-6FI-Vit D3, 1 α ,25(OH)₂-16-ene-23-yne-26,27-hexafluorocholecalciferol; KYN-54, 5-hydroxy-4-(2-phenyl-(E)-ethenyl)-2(5H)-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 $(100 - 100/\text{potency})$.

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 shortcut 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 obtained 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.