



HAL
open science

Most effective colon cancer chemopreventive agents in rats: a systematic review of aberrant crypt foci and tumor data, ranked by potency.

Denis E. Corpet, Sylviane Taché

► To cite this version:

Denis E. Corpet, Sylviane Taché. Most effective colon cancer chemopreventive agents in rats: a systematic review of aberrant crypt foci and tumor data, ranked by potency.. *Nutrition and Cancer*, 2002, 43 (1), pp.1-21. 10.1207/s15327914nc431_1 . hal-00284366

HAL Id: hal-00284366

<https://hal.science/hal-00284366>

Submitted on 9 Jun 2008

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

The authors are affiliated with the UMR Xénobiotiques, INRA ENVT, Université de Toulouse, 23 Capelles, 31076 Toulouse, France.

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).

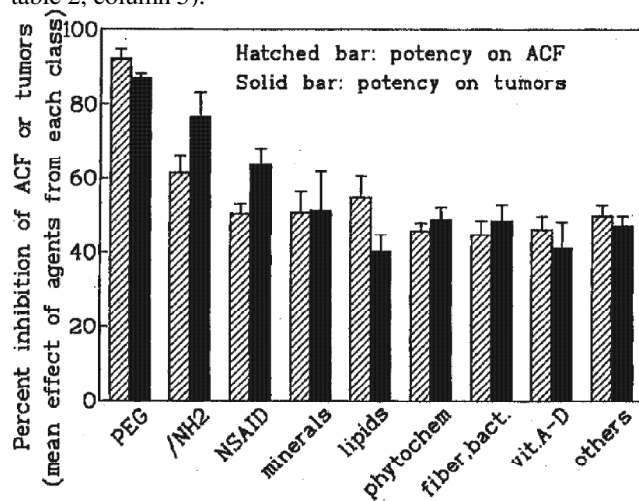


Figure 1. Mean potency of all chemopreventive agents in each class to reduce number of aberrant crypt foci (ACF) and tumor incidence in colon of rats. Nine classes are as follows: polyethylene glycol (PEG), difluoromethylornithine and amine modulators (/NH₂), nonsteroidal anti-inflammatory drugs (NSAID),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

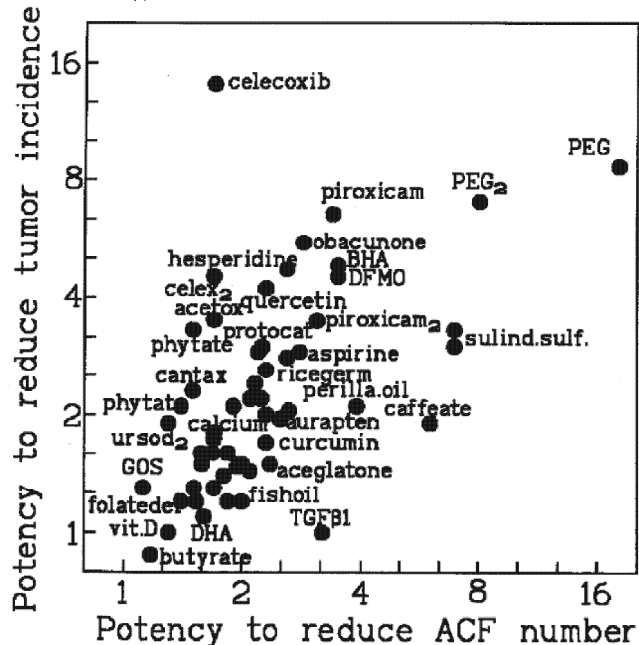


Figure 2. Correlation between potency of each agent to reduce number of ACF and to reduce incidence of tumors in colon of rats. Data from Tables 1 and 2 are shown on logarithmic scales. Points between 1.5 and 3 were too tight to be labeled. GOS, glucooigosaccharide; TGF- β 1, transforming growth factor- 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.

Acknowledgements and Notes

The authors thank Florence Corpet, for her help to build the website, and Giovanna Caderni for careful reading of the manuscript. Results were presented in part as a poster at the 2001 AACR meeting in New Orleans, and at the European Conference on Nutrition and Cancer in Lyon, France, June 2001. The authors are supported in part by the Direction Générale de l'Enseignement et de la Recherche du Ministère de l'Agriculture of France, and by the Institut National de la Recherche Agronomique of France.

Address reprint requests to Pr. D.E. Corpet, ENVT 23 Capelles, 31076 Toulouse, France. Fax: 33 561 491 263. E-mail: d.corpet AT envt.fr

Submitted 2 January 2002; accepted in final form 27 February 2002

References

1. Cummings JH, and Bingham SA: Fortnightly review - diet and the prevention of cancer. *Brit. Med. J.* 317, 1636-1640, 1998.
2. Alberts DS, Martinez ME, Roe DJ, GuillenRodriguez JM, Marshall JR, et al.: Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. *N. Engl. J. Med.* 342, 1156-1162, 2000.
3. BonithonKopp C, Kronborg O, Giacosa A, Rath U, and Faivre J: Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. *Lancet* 356, 1300-1306, 2000.
4. Greenberg ER, Baron JA, Tosteson TD, PonzdeLeon A, and Roncucci L: Antioxidant vitamins and colorectal adenoma. *New Engl. J. Med.* 331, 1720-1721, 1994.
5. McKeown-Eyssen G, Holloway C, Jazmaji V, Bright-See E, Dion P. et al.: A randomized trial of vitamins C and E in the prevention of recurrence of colorectal polyps. *Cancer Res.* 48, 4701-4705, 1988.
6. McKeown-Eyssen GE, Bright-See E, Bruce WR, Jazmaji V and Toronto-Polyp-Prevention-Group: A randomized trial of a low fat high fibre

- NUTRITION and CANCER, 2002, 43 (1), 1–21
 diet in the recurrence of colorectal polyps. *J. Clin. Epidemiol.* 47, 525-536, 1994.
7. MacLennan R, Macrae F, Bain C, Battistutta D, Chapuis P, et al.: Randomized trial of intake of fat, fiber, and beta carotene to prevent colorectal adenomas. *J. Natl Cancer Inst.* 87, 1760-1766, 1995.
 8. Schatzkin A, Lanza E, Corle D, Lance P, Iber F, et al.: Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N. Engl. J. Med.* 342, 1149-1155, 2000.
 9. Baron JA, Beach M, Mandel JS, Vanstolk RU, Haile RW, et al.: Calcium supplements for the prevention of colorectal adenomas. *N. Engl. J. Med.* 340, 101-107, 1999.
 10. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, et al.: The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N. Engl. J. Med.* 342, 1946-1952, 2000.
 11. Brasitus TA: Primary chemoprevention strategies for colorectal cancer: ursodeoxycholic acid and other agents. *Gastroenterology* 109, 2036-2038, 1995.
 12. Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, et al.: Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Brit. J. Urol.* 81, 730-734, 1998.
 13. Matsushashi N, Nakajima A, Fukushima Y, Yazaki Y, and Oka T: Effects of sulindac on sporadic colorectal adenomatous polyps. *Gut* 40, 344-349, 1997.
 14. Pasricha PJ, Bedi A, O'Connor K, et al.: The effects of sulindac on colorectal proliferation and apoptosis in familial adenomatous polyposis. *Gastroenterology* 109, 994-998, 1995.
 15. Ponz de Leon M, and Roncucci L: Chemoprevention of colorectal tumors: role of lactulose and of other agents. *Scand. J. Gastroenterol. Suppl.* 222, 72-5, 1997.
 16. Bird RP: Observation and quantification of aberrant crypts in murine colon treated with a colon carcinogen: preliminary findings. *Cancer Lett.* 37, 147-151, 1987.
 17. Bird RP: Role of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Cancer Lett.* 93, 55-71, 1995.
 18. Konstantakos AK, Siu IM, Pretlow TG, Stellato TA, and Pretlow TP: Human aberrant crypt foci with carcinoma in situ from a patient with sporadic colon cancer. *Gastroenterology* 111, 772-777, 1996.
 19. Pretlow TP, Siddiki B, Augenlicht LH, Pretlow TG, and Kim YS: Aberrant crypt foci (ACF) - earliest recognized players or innocent bystanders in colon carcinogenesis. in *Colorectal Cancer. Molecular mechanisms, premalignant state and its prevention.* Falk Sympos. 109. Schmiegel W. & Scholmerich J. Eds, Kluwer Academic Publishers, Dordrecht, The Netherlands. 109, (7) 1-16, 1999.
 20. Weisburger JH: Cover legend: Ranja P. Bird & W.R. Bob Bruce, and aberrant crypt foci ACF. *Cancer Res.* 58, 1, 1998.
 21. Yamada Y, Yoshimi N, Hirose Y, Matsunaga K, Katayama M, et al.: Sequential analysis of morphological and biological properties of beta-catenin-accumulated crypts, provable premalignant lesions independent of aberrant crypt foci in rat colon carcinogenesis. *Cancer Res.* 61, 1874-1878, 2001.
 22. Gold LS, Slone TH, Stern BR, Manley NB, and Ames BN: Rodent Carcinogens - Setting Priorities. *Science* 258, 261-265, 1992.
 23. Pence BC, Budding HF, and Yang SP: Multiple dietary factors in the enhancement of dimethylhydrazine carcinogenesis: Main effect of indole-3-carbinol. *J. Nat. Cancer Inst.* 77, 269-276, 1986.
 24. Perdigon G, Valdez JC, and Rachid M: Antitumor activity of yogurt: study of possible immune mechanisms. *J. Dairy Res* 65, 129-138, 1998.
 25. Steele VE, Moon RC, Lubet RA, Grubbs CJ, Reddy BS, et al.: Preclinical efficacy evaluation of potential chemopreventive agents in animal carcinogenesis models: methods and results from the NCI chemoprevention drug development program. *J. Cell. Biochem.* 32-54, 1994.
 26. Bajjal PK, Fitzpatrick DW, and Bird RP: Phenobarbital and 3-methylcholanthrene treatment alters phase I and II enzymes and the sensitivity of the rat colon to the carcinogenic activity of azoxymethane. *Food Chem. Toxicol.* 35, 789-798, 1997.
 27. Wargovich MJ, Jimenez A, Mckee K, Steele VE, Velasco M: Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and progression. *Carcinogenesis (Lond.)* 21, 1149-1155, 2000.
 28. Corpet DE, Parnaud G, Delverdier M, Peiffer G, and Tache S: Consistent and fast inhibition of colon carcinogenesis by polyethylene glycol in mice and rats given various carcinogens. *Cancer Res.* 60, 3160-3164, 2000.
 29. Parnaud G, Tache S, Peiffer G, and Corpet DE: Pluronic F68 block polymer, a very potent suppressor of carcinogenesis in the colon of rats and mice. *Brit. J. Cancer* 84, 90-93, 2001.
 30. Corpet DE, and Parnaud G: Polyethylene-glycol, a potent suppressor of azoxymethane-induced colonic aberrant crypt foci in rats. *Carcinogenesis (Lond.)* 20, 915-918, 1999.
 31. Komaki C, Okuno M, Onogi N, Moriwaki H, Kawamori T, et al.: Synergistic suppression of azoxymethane-induced foci of colonic aberrant crypts by the combination of beta-carotene and perilla oil in rats. *Carcinogenesis (Lond.)* 17, 1897-1901, 1996.
 32. Guo D, Schut HAJ, Davis CD, Snyderwine EG, Bailey GS, et al.: Protection by chlorophyllin and indole-3-carbinol against 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP)-induced DNA adducts and colonic aberrant crypts in the F344 rat. *Carcinogenesis (Lond.)* 16, 2931-2937, 1995.
 33. Parnaud G, Tache S, Peiffer G, and Corpet DE: Polyethylene-glycol suppresses colon cancer and causes dose-dependent regression of azoxymethane-induced aberrant crypt foci in rats. *Cancer Res.* 59, 5143-5147, 1999.
 34. Bak AW, McKnight W, Li P, et al, Wallace JL: Cyclooxygenase--independent chemoprevention with an aspirin derivative in a rat model of colonic adenocarcinoma. *Life Science* 62, 367-373, 1998.
 35. Rao CV, Desai D, Simi B, Kulkarni N, Amin S, et al.: Inhibitory effect of caffeic acid esters on azoxymethane-induced biochemical changes and aberrant crypt foci formation in rat colon. *Cancer Res.* 53, 4182-4188, 1993.
 36. Naigamwalla D, Chia MC, Tran TT, Medline A, Hay K, et al.: Polyethylene glycol 8000 and colon carcinogenesis: inhibition in the F344 rat, promotion in the min mouse. *Cancer Res.* 60, 6856-6858, 2000.
 37. Singletary KW, Medline B: Effect of grape seed proanthocyanidins on colon aberrant crypts and breast tumors in a rat dual-organ tumor model. *Nutr Cancer* 39, 252-258, 2001.
 38. Kohno H, Yoshitani S, Takashima S, Okumura A, Hosokawa M, et al.: Troglitazone, a ligand for peroxisome proliferator-activated receptor gamma, inhibits chemically-induced aberrant crypt foci in rats. *Jap J Cancer Res* 92, 396-403, 2001.
 39. Liew C, Schut HAJ, Chin SF, Pariza MW, and Dashwood RH: Protection of conjugated linoleic acids against IQ induced colon carcinogenesis in the F344 rat, a study of inhibitory mechanisms. *Carcinogenesis (Lond.)* 16: 3037-3043, 1995.
 40. Masaoka Y, Katoh O, and Watanabe H: Inhibitory effects of crude salts on the induction and development of colonic aberrant crypt foci in F-344 rats given azoxymethane. *Nutr. Cancer* 37, 78-81, 2000.
 41. Onogi N, Okuno M, Komaki C, Moriwaki H, Kawamori T, et al.: Suppressing effect of perilla oil on azoxymethane-induced foci of colonic aberrant crypts in rats. *Carcinogenesis (Lond.)* 17, 1291-1296, 1996.
 42. Rowland IR, Rumney CJ, Coutts JT, and Lieve LC: Effect of Bifidobacterium longum and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats. *Carcinogenesis (Lond.)* 19, 281-285, 1998.
 43. Wargovich MJ, Harris C, Chen CD, Palmer C, Steele VE, et al.: Growth kinetics and chemoprevention of aberrant crypts in the rat colon. *J. Cell. Biochem, Suppl.* 16G, 51-54, 1992.
 44. Wargovich MJ, Chen CD, Jimenez A, Steele VE, Velasco M, Stephens LC, et al.: Aberrant crypts as biomarker for colon cancer: evaluation of potential chemopreventive agents in the rat. *Cancer Epidemiol. Biomark. Prev.* 5, 355-360, 1996.
 45. Schmelz EM, Bushnev AS, Dillehay DL, Liotta DC, and Merrill AH: Suppression of aberrant colonic crypt foci by synthetic sphingomyelins with saturated or unsaturated sphingoid base backbones. *Nutr. Cancer* 28, 81-85, 1997.
 46. Fukutake M, Miura N, Yamamoto M, Fukuda K, Iijima O, et al.: Suppressive effect of the herbal medicine Oren-gedoku-to on cyclooxygenase-2 activity and azoxymethane-induced aberrant crypt foci development in rats. *Cancer Lett.* 157, 9-14, 2000.
 47. Schmelz EM, Dillehay DL, Webb SK, Reiter A, Adams J, et al.: Sphingomyelin consumption suppresses aberrant colonic crypt foci and increases the proportion of adenomas versus adenocarcinomas in CFI mice treated with 1,2-dimethylhydrazine: implications for dietary sphingolipids and colon carcinogenesis. *Cancer Res.* 56, 4936-4941, 1996.
 48. Mikhailowski R, Shpitz B, Polakcharon S, Kost Y, Segal C, et al.: Controlled release of TGF-beta(1) impedes rat colon carcinogenesis in vivo. *Intl. J. Cancer* 78, 618-623, 1998.
 49. Poulsen M, Molck AM, Thorup I, Breinholt V, Meyer O: The influence of simple sugars and starch given during pre- or post-initiation on aberrant crypt foci in rat colon. *Cancer Lett* 167, 135-143, 2001.
 50. Ishizuka S, and Kasai T: Inhibitory effect of dietary wheat bran on formation of aberrant crypt foci in rat colon induced by a single injection of 1,2-dimethylhydrazine. *Biosci. Biotechnol Biochem.* 60, 2084-2085, 1996.

51. Stamp D, Zhang XM, Medline A, Bruce WR, and Archer M: Sucrose enhancement of the early steps of colon carcinogenesis in mice. *Carcinogenesis (Lond.)* 14, 777-779, 1993.
52. Morishita Y, Yoshimi N, Kawabata K, Matsunaga K, Sugie S, et al.: Regressive effects of various chemopreventive agents on azoxymethane-induced aberrant crypt foci in the rat colon. *Jap. J. Cancer Res*, 88, 815-820, 1997.
53. Takahashi M, Minamoto T, Yamashita N, Yazawa K, Sugimura T, et al.: Reduction in formation and growth of 1,2-dimethylhydrazine-induced aberrant crypt foci in rat colon by docosahexanoic acid. *Cancer Res*, 53, 2786-2789, 1993.
54. Tanaka T, Maeda M, Kohno H, Murakami M, Kagami S et al.: Inhibition of azoxymethane-induced colon carcinogenesis in male F344 rats by the citrus limonoids obacunone and limonin. *Carcinogenesis (Lond.)* 22, 193-198, 2001.
55. Paulsen JE, Reistad R, Eliassen KA, Sjaastad OV, and Alexander J: Dietary polyamines promote the growth of azoxymethane-induced aberrant crypt foci in rat colon. *Carcinogenesis (Lond.)* 18, 1871-1875, 1997.
56. Mereto E, Frencia L, and Ghia M: Effect of aspirin on incidence and growth of aberrant crypt foci induced in the rat colon by 1,2-dimethylhydrazine. *Cancer Lett*, 76, 5-9, 1994.
57. Cassand P, Maziere S, Champ M, Meflah K, Bornet F, et al.: Effects of resistant starch- and vitamin a-supplemented diets on the promotion of precursor lesions of colon cancer in rats. *Nutr. Cancer* 27, 53-59, 1997.
58. Wargovich MJ, Chen CD, Harris C, Yang E, and Velasco M: Inhibition of aberrant crypt growth by non-steroidal anti-inflammatory agents and differentiation agents in the rat colon. *Intl. J. Cancer* 60, 515-519, 1995.
59. Takahashi M, Totsuka Y, Masuda M, Fukuda K, Oguri A, et al.: Reduction in formation of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-induced aberrant crypt foci in the rat colon by docosahexanoic acid (DHA). *Carcinogenesis (Lond.)* 18, 1937-1941, 1997.
60. Nagai T, Ishizuka S, Hara H, and Aoyama Y: Dietary sugar beet fiber prevents the increase in aberrant crypt foci induced by gamma-irradiation in the colorectum of rats treated with an immunosuppressant. *J. Nutr*, 130, 1682-1687, 2000.
61. Li W, Wanibuchi H, Salim EI, Wei M, Yamamoto S, et al.: Inhibition by ginseng of 1,2-dimethylhydrazine induction of aberrant crypt foci in the rat colon. *Nutr. Cancer* 36, 66-73, 2000.
62. GaliMuhtasib HU, Younes IH, Karchesy JK, ElSabban ME: Plant tannins inhibit the induction of aberrant crypt foci and colonic tumors by DMH in mice. *Nutr Cancer* 39, 108-116, 2001.
63. Tanaka T, Makita H, Kawabata K, Mori H, Kakumoto M, et al.: Chemoprevention of azoxymethane-induced rat colon carcinogenesis by the naturally occurring flavonoids, diosmin and hesperidin. *Carcinogenesis (Lond.)* 18, 957-965, 1997.
64. Kristiansen E, Thorup I, and Meyer O: Influence of different diets on development of DMH-induced aberrant crypt foci and colon tumor incidence in wistar rats. *Nutr. Cancer* 23, 151-159, 1995.
65. Abdelali H, Cassand P, Soussotte V, Daubeze M, Bouley C, et al.: Effect of dairy products on initiation of precursor lesions of colon cancer in rats. *Nutr. Cancer* 24, 121-132, 1995.
66. Kawamori T, Elbayoumy K, Ji BY, Rodriguez JGR, Rao CV, et al.: Evaluation of benzyl selenocyanate glutathione conjugate for potential chemopreventive properties in colon carcinogenesis. *Intl. J. Oncol*, 13, 29-34, 1998.
67. Schmelz EM, Sullards MC, Dillehay DL, and Merrill AH: Colonic cell proliferation and aberrant crypt foci formation are inhibited by dairy glycosphingolipids in 1,2-dimethylhydrazine-treated CF1 mice. *J. Nutr*, 130, 522-527, 2000.
68. Matsunaga K, Iijima H, and Kobayashi H: Neonatal inoculation with the protein-bound polysaccharide PSK increases resistance of adult animals to challenge with syngeneic tumor cells and reduces azoxymethane-induced precancerous lesions in the colon. *Cancer Epidemiol. Biomark. Prev*, 9, 1313-1322, 2000.
69. Xu M, Bailey AC, Hernaez JF, Taoka CR, Schut HAJ, et al.: Protection by green tea, black tea, and indole-3-carbinol against 2-amino-3-methylimidazo[4,5-f]quinoline-induced DNA adducts and colonic aberrant crypts in the F344 rat. *Carcinogenesis (Lond.)* 17, 1429-1434, 1996.
70. Weisburger JH, Rivenson A, Garr K, and Aliaga C: Tea, or tea and milk, inhibit mammary gland and colon carcinogenesis in rats. *Cancer Lett*, 114, 323-327, 1997.
71. Matsukawa Y, Nishino H, Okuyama Y, Matsui T, Matsumoto T, et al.: Effects of quercetin and/or restraint stress on formation of aberrant crypt foci induced by azoxymethane in rat colons. *Oncology* 54, 118-121, 1997.
72. Yoshimi N, Qiao Z, Matsunaga K, Mori H, Hanausek M, et al.: The modifying effects of aceglatone, a B-glucuronidase inhibitor, in colon carcinogenesis of F344 rats. *Proc. Am. Assoc. Cancer Res*, 42, #957 (abstr), 2001.
73. Zheng Y, Kramer PM, Olson G, Lubet A, Steele VE, et al.: Prevention by retinoids of azoxymethane-induced tumors and aberrant crypt foci and their modulation of cell proliferation in the colon of rats. *Carcinogenesis (Lond.)* 18, 2119-2125, 1997.
74. Kawabata K, Tanaka T, Murakami T, Okada T, Murai H, et al.: Dietary prevention of azoxymethane-induced colon carcinogenesis with rice-germ in F344 rats. *Carcinogenesis (Lond.)* 20, 2109-2115, 1999.
75. Rao CV, Simi B, and Reddy BS: Inhibition by dietary curcumin of azoxymethane-induced ornithine decarboxylase, tyrosine protein kinase, arachidonic acid metabolism and aberrant crypt foci formation in the rat colon. *Carcinogenesis (Lond.)* 14, 2219-2225, 1993.
76. Metz N, Lobstein A, Schneider Y, Gosse F, Schleiffer R, et al.: Suppression of azoxymethane-induced preneoplastic lesions and inhibition of cyclooxygenase-2 activity in the colonic mucosa of rats drinking a crude green tea extract. *Nutr. Cancer* 38, 60-64, 2000.
77. Rao CV, Kawamori T, Hamid R, and Reddy BS: Chemoprevention of colonic aberrant crypt foci by an inducible nitric oxide synthase-selective inhibitor. *Carcinogenesis (Lond.)* 20, 641-644, 1999.
78. Tanaka T, Kawabata K, Kakumoto M, Makita H, Hara A, et al.: Citrus auraptene inhibits chemically induced colonic aberrant crypt foci in male F344 rats. *Carcinogenesis (Lond.)* 18, 2155-2161, 1997.
79. Seraj MJ, Umamoto A, Kajikawa A, Mimura S, Kinouchi T, et al.: Effects of dietary bile acids on formation of azoxymethane-induced aberrant crypt foci in F344 rats. *Cancer Lett*, 115, 97-103, 1997.
80. Feng Y, Finley JW, Davis CD, Becker WK, Fretland AJ, et al.: Dietary selenium reduces the formation of aberrant crypts in rats administered 3,2'-dimethyl-4-aminobiphenyl. *Toxicol. Applied Pharmacol*, 157, 36-42, 1999.
81. Kohno H, Yoshitani S, Tsukio Y, Murakami A, Koshimizu K, et al.: Dietary administration of citrus nobletin inhibits azoxymethane-induced colonic aberrant crypt foci in rats. *Life Sciences* 69, 901-913, 2001.
82. Finley JW, Davis CD, and Feng Y: Selenium from high selenium broccoli protects rats from colon cancer. *J. Nutr*, 130, 2384-2389, 2000.
83. Hatono S Jimenez A, Wargovich MJ: Chemopreventive effect of S-allylcysteine and its relationship to the detoxification enzyme glutathione S-transferase. *Carcinogenesis (Lond.)* 17, 1041-4, 1996.
84. Dillehay DL, Webb SK, Schmelz EM, and Merrill AH: Dietary sphingomyelin inhibits 1,2-dimethylhydrazine-induced colon cancer in CF1 mice. *J. Nutr*, 124, 615-620, 1994.
85. Kawamori T, Tanaka T, Kojima T, Suzui M, Ohnishi M, et al.: Suppression of azoxymethane-induced rat colon aberrant crypt foci by dietary protocatechuic acid. *Jap. J. Cancer Res*, 85, 686-691, 1994.
86. Zheng Y, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, et al.: Effect of retinoids on AOM-induced colon cancer in rats: modulation of cell proliferation, apoptosis and aberrant crypt foci. *Carcinogenesis (Lond.)* 20, 255-260, 1999.
87. Kulkarni N, and Reddy BS: Inhibitory effect of *Bifidobacterium longum* cultures on the azoxymethane-induced aberrant crypt foci formation and fecal bacterial beta-glucuronidase. *Proc. Soc. Exp. Biol. Med*, 207, 278-283, 1994.
88. AviviGreen C, Madar Z, and Schwartz B: Apoptosis-cascade proteins are regulated in vivo by high intracolonic butyrate concentration: correlation with colon cancer inhibition. *Oncol. Res*, 12, 83-95, 2000.
89. Rao CV, Newmark HL, and Reddy BS: Chemopreventive effect of squalene on colon cancer. *Carcinogenesis (Lond.)* 19, 287-290, 1998.
90. Masaoka Y, Watanabe H, Katoh O, Ito A, and Dohi K: Effects of miso and NaCl on the development of colonic aberrant crypt foci induced by azoxymethane in F344 rats. *Nutr. Cancer* 32, 25-28, 1998.
91. Hirose M, Yamaguchi T, Lin C, Kimoto N, Futakuchi M, et al.: Effects of arctiin on PhIP-induced mammary, colon and pancreatic carcinogenesis in female sprague-dawley rats and MeIQx-induced hepatocarcinogenesis in male F344 rats. *Cancer Lett*, 155, 79-88, 2000.
92. Davis CD, and Feng Y: Dietary copper, manganese and iron affect the formation of aberrant crypts in colon of rats administered 3,2'-dimethyl-4-aminobiphenyl. *J. Nutr*, 129, 1060-1067, 1999.
93. Narisawa T, Fukaura Y, Hasebe M, Ito M, Aizawa R, et al.: Inhibitory effects of natural carotenoids, alpha-carotene, beta-carotene, lycopene and lutein, on colonic aberrant crypt foci formation in rats. *Cancer Lett*, 107, 137-142, 1996.
94. Finley JW, Ip C, Lisk DJ, Davis CD, Hintze KJ, et al.: Cancer-protective properties of high-selenium broccoli. *J Agric Food Chem* 49, 2679-2683, 2001.

95. Latham P, Lund EK, and Johnson IT: Dietary n-3 PUFA increases the apoptotic response to 1,2-dimethylhydrazine, reduces mitosis and suppresses the induction of carcinogenesis in the rat colon. *Carcinogenesis (Lond.)* 20, 645-650, 1999.
96. Rao CV, Cooma I, Swamy MV, Simi B, and Reddy BS: Modulation of inducible nitric oxide synthase and cyclooxygenase activities by curcumin during different stages of experimental colon carcinogenesis. *Proc. Am. Assoc. Cancer Res*, 42, #03084 (abstr), 2001.
97. Rao CV, Hirose Y, Indranie C, and Reddy BS: Modulation of experimental colon tumorigenesis by types and amounts of dietary fatty acids. *Cancer Res*, 61, 1927-1933, 2001.
98. Challa A, Rao DR, Chawan CB, and Shackelford L: Bifidobacterium longum and lactulose suppress azoxymethane-induced colonic aberrant crypt foci in rats. *Carcinogenesis (Lond.)* 18, 517-521, 1997.
99. Thiagarajan DG, Bennink MR, Bourquin LD, and Kavas FA: Prevention of precancerous colonic lesions in rats by soy flakes, soy flour, genistein, and calcium. *Am. J. Clin. Nutr.* 68, 1394S-1399S, 1998.
100. Duranton B, Nsiemvo E, Schleiffer R, Gosse F, Galluser M, et al.: Suppression of preneoplastic changes in the intestine of rats fed low levels of polyamines. *Cancer Res*, 57, 573-575, 1997.
101. Pereira MA, and Khoury MD: Prevention by chemopreventive agents of azoxymethane-induced foci of aberrant crypts in rat colon. *Cancer Lett*, 61, 27-33, 1991.
102. Fukutake M, Yokota S, Kamamura H, Iizuka A, Amagaya S, et al.: Inhibitory effect of coptidis rhizoma and scutellariae radix on azoxymethane-induced aberrant crypt foci formation in rat colon. *Biol. Pharm. Bull.* 21, 814-817, 1998.
103. Tanaka T, Shimizu M, Kohno H, Yoshitani S, Tsukio Y, et al.: Chemoprevention of azoxymethane-induced rat aberrant crypt foci by dietary zerumbone isolated from zingiber zerumbet. *Life Sciences* 69, 1935-1945, 2001.
104. Shivapurkar N, Tang ZC, Frost A, and Alabaster O: Inhibition of progression of aberrant crypt foci and colon tumor development by vitamin E and beta-carotene in rats on a high-risk diet. *Cancer Lett*, 91, 125-132, 1995.
105. Perrin P, Pierre F, Patry Y, Champ M, Berreur M, et al.: Only fibres promoting a stable butyrate producing colonic ecosystem decrease the rate of aberrant crypt foci in rats. *Gut* 48, 53-61, 2001.
106. Taniyama T, Wanibuchi H, Salim EL, Yano Y, Otani S, et al.: Chemopreventive effect of 24r,25-dihydroxyvitamin d-3 in N,N'-dimethylhydrazine-induced rat colon carcinogenesis. *Carcinogenesis (Lond.)* 21, 173-178, 2000.
107. Koo M, and Rao AV: Long-Term Effect of Bifidobacteria and Neosugar on Precursor Lesions of Colonic Cancer in CFI Mice. *Nutr. Cancer* 16, 249-257, 1991.
108. Tanaka T, Kawabata K, Kakumoto M, Hara A, Murakami A, et al.: Citrus auraptene exerts dose-dependent chemopreventive activity in rat large bowel tumorigenesis: the inhibition correlates with suppression of cell proliferation and lipid peroxidation and with induction of phase II drug-metabolizing enzymes. *Cancer Res*, 58, 2550-2556, 1998.
109. Pereira MA, Barnes LH, Rassman VL, Kelloff GV, and Steele VE: Use of azoxymethane-induced foci of aberrant crypts in rat colon to identify potential cancer chemopreventive agents. *Carcinogenesis (Lond.)* 15, 1049-1054, 1994.
110. Narisawa T, Fukaura Y, Hasebe M, Nomura S, Oshima S, et al.: Prevention of n-methylnitrosourea-induced colon carcinogenesis in rats by oxygenated carotenoid capsanthin and capsanthin-rich paprika juice. *Proc. Soc. Exp. Biol. Med.* 224, 116-122, 2000.
111. Charalambous D, Farmer C, and O'Brien PE: Sulindac and indomethacin inhibit formation of ACF in the colon of DMH treated rats. *J. Gastroenterol. Hepatol.* 11, 88-92, 1996.
112. Suaeyun R, Kinouchi T, Arimochi H, Vinitketkumnuen U, and Ohnishi Y: Inhibitory effects of lemon grass (*Cymbopogon citratus* Stapf) on formation of azoxymethane-induced DNA adducts and aberrant crypt foci in the rat colon. *Carcinogenesis (Lond.)* 18, 949-955, 1997.
113. Han BS, Park CB, Takasuka N, Naito A, Sekine K, et al.: A ferulic acid derivative, ethyl 3-(4'-geranyloxy-3-methoxyphenyl)-2-propenoate, as a new candidate chemopreventive agent for colon carcinogenesis in the rat. *Japan J Cancer Res* 92, 404-409, 2001.
114. Reddy BS, Rao CV, and Seibert K: Evaluation of cyclooxygenase-2 inhibitor for potential chemopreventive properties in colon carcinogenesis. *Cancer Res*, 56, 4566-4569, 1996.
115. Smith TK, Lund EK, and Johnson IT: Inhibition of dimethylhydrazine-induced aberrant crypt foci and induction of apoptosis in rat colon following oral administration of the glucosinolate sinigrin. *Carcinogenesis (Lond.)* 19, 267-273, 1998.
116. Tanaka T, Makita H, Kawamori T, Kawabata K, Mori H, et al.: A xanthine oxidase inhibitor 1'-acetoxychavicol acetate inhibits azoxymethane-induced colonic aberrant crypt foci in rats. *Carcinogenesis (Lond.)* 18, 1113-1118, 1997.
117. Jia X, Han C: Effects of green tea on colonic aberrant crypt foci and proliferative indexes in rats. *Nutr. Cancer*. 39, 239-243, 2001.
118. Lam LKT, and Zhang JL: Reduction of aberrant crypt formation in the colon of CFI mice by potential chemopreventive agents. *Carcinogenesis (Lond.)* 12, 2311-2315, 1991.
119. Yoshimi N, Matsunaga K, Katayama M, Yamada Y, Kuno T, et al.: The inhibitory effects of mangiferin, a naturally occurring glucosylxanthone, in bowel carcinogenesis of male F344 rats. *Cancer Lett* 163, 163-170, 2001.
120. Tanaka T, Kohno H, Shimada R, Kagami S, Yamaguchi F, et al.: Prevention of colonic aberrant crypt foci by dietary feeding of garcinol in male F344 rats. *Carcinogenesis (Lond.)* 21, 1183-1189, 2000.
121. Wargovich MJ, Woods C, Liao J, Hollis D, Marquart L, et al.: Calcium fortified whole grain diet inhibits aberrant crypt foci in the rat colon. *Proc. Am. Assoc. Cancer Res*, 42, #949 (abstr), 2001.
122. Rao CV, Chou D, Simi B, Ku HC, and Reddy BS: Prevention of colonic aberrant crypt foci and modulation of large bowel microbial activity by dietary coffee fiber, inulin and pectin. *Carcinogenesis (Lond.)* 19, 1815-1819, 1998.
123. Young GP, Mcintyre A, Albert V, Folino M, Muir JG, et al.: Wheat bran suppresses potato starch-potentiated colorectal tumorigenesis at the aberrant crypt stage in a rat model. *Gastroenterology* 110, 508-514, 1996.
124. Takahashi M, Fukutake M, Isoi T, Fukuda K, Sato H, et al.: Suppression of azoxymethane-induced rat colon carcinoma development by a fish oil component, docosahexaenoic acid (DHA). *Carcinogenesis (Lond.)* 18, 1337-1342, 1997.
125. Yu Z, Xu M, Santanarios G, Shen R, Izquierdopolido M, et al.: A comparison of whole wheat, refined wheat and wheat bran as inhibitors of heterocyclic amines in the salmonella mutagenicity assay and in the rat colonic aberrant crypt focus assay. *Food Chem Toxicol* 39, 655-665, 2001.
126. Tsuda H, Park, CB, et al.: Influence of ethyl-geranyloxy-methoxyphenyl-propenoate (EGMP) on early stage colon carcinogenesis in rats treated with azoxymethane (AOM). *Anticancer Res*, 19, 3779-3782, 1999.
127. Luceri C, Caderni G, Lancioni L, Aiolfi S, Dolara P, et al.: Effects of repeated boluses of sucrose on proliferation and on AOM-induced aberrant crypt foci in rat colon. *Nutr. Cancer* 25, 187-196, 1996.
128. Kim DJ, Kang JS, Ahn B, Kim KS, Park KH, et al.: Chemopreventive effect of 2-(allylthio)pyrazine (2-AP) on rat colon carcinogenesis induced by azoxymethane (AOM). *Cancer Lett* 166, 125-133, 2001.
129. Tanaka T, Kohno H, Yoshitani S, Takashima S, Okumura A, et al.: Ligands for peroxisome proliferator-activated receptors alpha and gamma inhibit chemically induced colitis and formation of aberrant crypt foci in rats. *Cancer Res* 61, 2424-2428, 2001.
130. Schmelz EM, Bushnev AS, Dillehay DL, Sullards MC, Liotta DC, et al.: Ceramide-beta-d-glucuronide: synthesis, digestion, and suppression of early markers of colon carcinogenesis. *Cancer Res*, 59, 5768-5772, 1999.
131. Paulsen JE, Stamm T, and Alexander JA: Fish oil-derived concentrate enriched in eicosapentaenoic and docosahexaenoic acid as ethyl esters inhibits the formation and growth of aberrant crypt foci in rat colon. *Pharmacol. Toxicol.* 82: 28-33, 1998.
132. Kawamori T, Tanaka T, Hara A, Yamahara J, and Mori H: Modifying effects of naturally occurring products on the development of colonic aberrant crypt foci induced by azoxymethane in F344 rats. *Cancer Res*, 55, 1277-1282, 1995.
133. Takahashi M, Fukutake M, Yokota S, Ishida K, Wakabayashi K, et al.: Suppression of azoxymethane-induced aberrant crypt foci in rat colon by nimesulide, a selective inhibitor of cyclooxygenase 2. *J. Cancer Res. Clin. Oncol.* 122, 219-222, 1996.
134. Reddy BS, Hamid R, and Rao CV: Effect of dietary oligofructose and inulin on colonic preneoplastic aberrant crypt foci inhibition. *Carcinogenesis (Lond.)* 18, 1371-1374, 1997.
135. Chung FL, Conaway CC, Rao CV, and Reddy BS: Chemoprevention of colonic aberrant crypt foci in Fischer rats by sulforaphane and phenethyl isothiocyanate. *Carcinogenesis (Lond.)* 21, 2287-2291, 2000.
136. Steele VE, Bagheri D, Balentine DA, Boone CW, Mehta R, et al.: Preclinical efficacy studies of green and black tea extracts. *Proc. Soc. Exp. Biol. Med.* 220, 210-212, 1999.
137. Ferguson LR, and Harris PJ: Suberized plant cell walls suppress formation of heterocyclic amine-induced aberrant crypts in a rat model. *Chemico - Biological Interactions* 114, 191-209, 1998.
138. Harris GK, Carlton PS, Liston BW, Gupta AK, and Stoner GD: Inhibitory effects of freeze-dried black raspberries on AOM induced colon

- cancer in the F344 rat. *Proc. Am. Assoc. Cancer Res*, 42, #948 (abstr), 2001.
139. Maziere S, Meflah K, Tavan E, Champ M, Narbonne JF, et al.: Effect of resistant starch and/or fat-soluble vitamins A and E on the initiation stage of aberrant crypts in rat colon. *Nutr. Cancer* 31, 168-177, 1998.
140. Challa A, Rao DR, and Reddy BS: Interactive suppression of aberrant crypt foci induced by azoxymethane in rat colon by phytic acid and green tea. *Carcinogenesis (Lond.)* 18, 2023-2026, 1997.
141. Tanaka T, Kawamori T, Ohnishi M, Makita H, Mori H, et al.: Suppression of azoxymethane-induced rat colon carcinogenesis by dietary administration of naturally occurring xanthophylls astaxanthin and canthaxanthin during the postinitiation phase. *Carcinogenesis (Lond.)* 16, 2957-2963, 1995.
142. Chewonarin T, Kinouchi T, Kataoka K, Arimochi H, Kuwahara T, et al.: Effects of roselle (*Hibiscus sabdariffa* linn.), a thai medicinal plant, on the mutagenicity of various known mutagens in *Salmonella typhimurium* and on formation of aberrant crypt foci induced by the colon carcinogens azoxymethane and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in F344 rats. *Food Chem. Toxicol.* 37, 591-601, 1999.
143. Kawamori T, Tanaka T, Hirose Y, Ohnishi M, and Mori H: Inhibitory effects of d-limonene on the development of colonic aberrant crypt foci induced by azoxymethane in F344 rats. *Carcinogenesis (Lond.)* 17, 369-372, 1996.
144. Watanabe K, Kawamori T, Nakatsugi S, Ohta T, Ohuchida S, et al.: Inhibitory effect of a prostaglandin E receptor subtype EPI selective antagonist, ONO-8713, on development of azoxymethane-induced aberrant crypt foci in mice. *Cancer Lett.* 156, 57-61, 2000.
145. Thorup I, Meyer O, and Kristiansen E: Effect of potato starch, cornstarch and sucrose on aberrant crypt foci in rats exposed to azoxymethane. *Anticancer Res.* 15, 2101-2105, 1995.
146. Kim JM, Araki S, Kim DJ, Park CB, Takasuka N, et al.: Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1,2-dimethylhydrazine initiation. *Carcinogenesis (Lond.)* 19, 81-85, 1998.
147. Kawamori T, Takahashi M, Watanabe K, Ohta T, Nakatsugi S, et al.: Suppression of azoxymethane-induced colonic aberrant crypt foci by a nitric oxide synthase inhibitor. *Cancer Lett.* 148, 33-37, 2000.
148. Arimochi H, Kinouchi T, Kataoka K, Kuwahara T, and Ohnishi Y: Effect of intestinal bacteria on formation of azoxymethane-induced aberrant crypt foci in the rat colon. *Biochem. Biophys. Res. Com.* 238, 753-757, 1997.
149. Yoshimi N, Kawabata K, Hara A, Matsunaga K, Yamada Y, et al.: Inhibitory effect of NS-398, a selective cyclooxygenase-2 inhibitor, on azoxymethane-induced aberrant crypt foci in colon carcinogenesis of F344 rats. *Jap. J. Cancer Res.* 88, 1044-1051, 1997.
150. Jenab M, and Thompson LU: The influence of phytic acid in wheat bran on early biomarkers of colon carcinogenesis. *Carcinogenesis (Lond.)* 19, 1087-1092, 1998.
151. Li H, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, et al.: Effect of calcium on azoxymethane-induced aberrant crypt foci and cell proliferation in the colon of rats. *Cancer Lett.* 124, 39-46, 1998.
152. Gallaher DD, and Khil J: The effect of synbiotics on colon carcinogenesis in rats. *J. Nutr.* 129, 1483S-1487S, 1999.
153. Agarwal B, Rao CV, Bhendwal S, Ramey WR, Shirin H, et al.: Lovastatin augments sulindac-induced apoptosis in colon cancer cells and potentiates chemopreventive effects of sulindac. *Gastroenterology* 117, 838-847, 1999.
154. Leleu RK, Young GP, and McIntosh GH: Folate deficiency diminishes the occurrence of aberrant crypt foci in the rat colon but does not alter global DNA methylation status. *J. Gastroenterol. Hepatol.* 15, 1158-1164, 2000.
155. Salim EI, Wanibuchi H, Taniyama T, Yano Y, Morimura K, et al.: Inhibition of development of n,n'-dimethylhydrazine-induced rat colonic aberrant crypt foci by pre, post and simultaneous treatments with 24r,25-dihydroxyvitamin d-3. *Jap. J. Cancer Res.* 88, 1052-1062, 1997.
156. Ikegami T, Matsuzaki Y, Shoda J, Kano M, Hirabayashi N, et al.: The chemopreventive role of ursodeoxycholic acid in azoxymethane-treated rats: suppressive effects on enhanced group II phospholipase a(2) expression in colonic tissue. *Cancer Lett.* 134, 129-139, 1998.
157. Morotomi M, Sakaitani Y, Satou M, Takahashi T, Takagi A, et al.: Effects of a high-fat diet on azoxymethane-induced aberrant crypt foci and fecal biochemistry and microbial activity in rats. *Nutr. Cancer* 27, 84-91, 1997.
158. Arimochi H, Kataoka K, Kuwahara T, Nakayama H, Misawa N, et al.: Effects of beta-glucuronidase-deficient and lycopene-producing *Escherichia coli* strains on formation of azoxymethane-induced aberrant crypt foci in the rat colon. *Biochem. Biophys. Res. Com.* 262, 322-327, 1999.
159. Jenab M, and Thompson LU: The influence of flaxseed and lignans on colon carcinogenesis and beta-glucuronidase activity. *Carcinogenesis (Lond.)* 17, 1343-1348, 1996.
160. Pretlow TP, Oriordan MA, Somich GA, Amini SB, and Pretlow TG: Aberrant crypts correlate with tumor incidence in F344 rats treated with azoxymethane and phytate. *Carcinogenesis (Lond.)* 13, 1509-1512, 1992.
161. Caderni G, Luceri C, Lancioni L, Tessitore L, and Dolara P: Slow-release pellets of sodium butyrate increase apoptosis in the colon of rats treated with azoxymethane, without affecting aberrant crypt foci and colonic proliferation. *Nutr. Cancer* 30, 175-181, 1998.
162. Baines AT, Holubec H, Basye JL, Thorne P, Bhattacharyya AK, et al.: The effects of dietary selenomethionine on polyamines and azoxymethane-induced aberrant crypts. *Cancer Lett* 160, 193-198, 2000.
163. Wijnands MVW, Schoterman HC, Bruijntjes JP, Hollanders VMH, and Woutersen RA: Effect of dietary galacto-oligosaccharides on azoxymethane-induced aberrant crypt foci and colorectal cancer in Fischer 344 rats. *Carcinogenesis (Lond.)* 22, 127-132, 2001.
164. Jain CK, Agarwal S, and Rao AV: The effect of dietary lycopene on bioavailability, tissue distribution, in vivo antioxidant properties and colonic preneoplasia in rats. *Nutr. Res.* 19, 1383-1391, 1999.
165. Rijken PJ, Timmer WG, Vandekooij AJ, Vanbenschoop IM, Wiseman SA, et al.: Effect of vegetable and carotenoid consumption on aberrant crypt multiplicity, a surrogate end-point marker for colorectal cancer in azoxymethane-induced rats. *Carcinogenesis (Lond.)* 20, 2267-2272, 1999.
166. Kawamori T, Rao CV, Seibert K, and Reddy BS: Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, against colon carcinogenesis. *Cancer Res.* 58, 409-412, 1998.
167. Reddy BS, and Rivenson A: Inhibitory effect of *Bifidobacterium longum* on colon, mammary, and liver carcinogenesis induced by 2-amino-3-methylimidazo[4,5-f]quinoline, a food mutagen. *Cancer Res.* 53, 3914-3918, 1993.
168. StClair WH, Billings PC, Carew JA, KellerMcGandy C, Newberne PM, et al.: Suppression of dimethylhydrazine-induced carcinogenesis in mice by dietary addition of the Bowman-Birk protease inhibitor. *Cancer Res.* 50, 580-586, 1990.
169. Rao CV, Tokumo K, Rigotty J, Zang E, Kelloff G, et al.: Chemoprevention of colon carcinogenesis by dietary administration of piroxicam, alpha-difluoromethylornithine, 16alpha-fluoro-5-androsten-17-one, and ellagic acid individually and in combination. *Cancer Res.* 51, 4528-4534, 1991.
170. Kawamori T, Tanaka T, Ohnishi M, Hirose Y, Nakamura Y, et al.: Chemoprevention of azoxymethane-induced colon carcinogenesis by dietary feeding of s-methyl methane thiosulfonate in male F344 rats. *Cancer Res.* 55, 4053-4058, 1995.
171. Weed HG, McGandy RB, and Kennedy AR: Protection against dimethylhydrazine-induced adenomatous tumors of the mouse colon by the dietary addition of an extract of soybeans containing the Bowman-Birk protease inhibitor. *Carcinogenesis (Lond.)* 6, 1239-1241, 1985.
172. Kim YI, Salomon RN, Graemecook F, Choi SW, Smith DE, et al.: Dietary folate protects against the development of macroscopic colonic neoplasia in a dose responsive manner in rats. *Gut* 39, 732-740, 1996.
173. Li H, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, et al.: Termination of piroxicam treatment and the occurrence of azoxymethane-induced colon cancer in rats. *Cancer Lett.* 147, 187-193, 1999.
174. Reddy BS: Dietary fiber and colon cancer: animal model studies. *Preventive Med.* 16, 559-565, 1987.
175. Li H, Schut HAJ, Conran P, Kramer PM, Lubet RA, et al.: Prevention by aspirin and its combination with alpha-difluoromethylornithine of azoxymethane-induced tumors, aberrant crypt foci and prostaglandin E-2 levels in rat colon. *Carcinogenesis (Lond.)* 20, 425-430, 1999.
176. Mori H, Morishita Y, Shinoda T, and Tanaka T: Preventive effects of magnesium hydroxide on carcinogen-induced large bowel carcinogenesis in rats. *Basic Life Sci* 61, 111-118, 1993.
177. Disilvestro RA, Greenson JK, and Liao ZM: Effects of low copper intake on dimethylhydrazine-induced colon cancer in rats. *Proc. Soc. Exp. Biol. Med.* 201, 94-97, 1992.
178. Dwivedi C, Oredipe OA, Barth RE, Downie AA, and Webb TE: Effects of the experimental chemopreventative agent, glucarate, on intestinal carcinogenesis in rats. *Carcinogenesis (Lond.)* 10, 1539-1541, 1989.
179. Goldin BR, and Gorbach SL: Effect of antibiotics on incidence of rat intestinal tumors induced by 1-2, dimethylhydrazine dihydrochloride. *J. Nat. Cancer Inst.* 67, 877-880, 1981.
180. Reddy BS, Maura Y, Weisburger JH: Effect of various levels of dietary butylated hydroxyanisole on methylazoxymethanol acetate induced colon carcinogenesis in CFI mice. *J. Nat. Cancer Inst.* 71, 1299-1305, 1983.

181. Reddy BS, Narisawa T, Wtigh P, Vukusich D, Weisburger JH, et al.: Colon carcinogenesis with azoxymethane and dimethylhydrazine in germ-free rats. *Cancer Res*, 35, 287-290, 1975.
182. Reddy BS, Hirose Y, Lubet R, Steele V, Kelloff G, et al.: Chemoprevention of colon cancer by specific cyclooxygenase-2 inhibitor, celecoxib, administered during different stages of carcinogenesis. *Cancer Res*, 60, 293-297, 2000.
183. Deschner EE, Ruperto J, Wong G, and Newmark HL: Quercetin and rutin as inhibitors of azoxymethane-induced colonic neoplasia. *Carcinogenesis (Lond.)* 12, 1193-1196, 1991.
184. Nutter RL, Gridley DS, Kettering JD, Goude AG, and Slater JM: BALB/c mice fed milk or beef protein: differences in response to 1,2-dimethylhydrazine carcinogenesis. *J. Natl. Cancer Inst*, 71, 867-874, 1983.
185. Kritchevsky D, and Klurfeld DM: Interaction of fiber and energy restriction in experimental colon carcinogenesis. *Cancer Lett*, 114, 51-52, 1997.
186. Hakkak R, Korourian S, Ronis MJ J, Johnston JM, Badger TM: Soy protein isolate consumption protects against azoxymethane-induced colon tumors in male rats. *Cancer Lett* 166, 27-32, 2001.
187. Davis AE, and Patterson F: Aspirin reduces the incidence of colonic carcinoma in the dimethylhydrazine rat animal model. *Austr. N. Zeal. J. Med*, 24, 301-303, 1994.
188. Reddy BS, and Maehara Y: Tumor promotion by dietary fat in azoxymethane-induced colon carcinogenesis in female F344 rats: influence of amount and source of dietary fat. *J. Natl. Cancer Inst*, 72: 745-750, 1984.
189. Tanaka T, Kawabata K, Kakumoto M, Makita H, Matsunaga K, et al.: Chemoprevention of azoxymethane-induced rat colon carcinogenesis by a xanthine oxidase inhibitor, 1'-acetoxychavicol acetate. *Jap. J. Cancer Res*, 88, 821-830, 1997.
190. Rao AV, Goettler DM, and Bird RP: The effect of a low-risk diet on tumor incidence in chemically induced colon cancer in rats. *Nutr. Cancer* 11, 11-20, 1988.
191. Wali RK, Bissonnette M, Khare S, Hart J, Sitrin MD, et al.: 1 alpha,25--dihydroxy-16-ene-23-yne-26,27-hexafluorocholecalciferol, a noncalcemic analogue of vitamin D3, inhibits azoxymethane induced colonic tumorigenesis. *Cancer Res*, 55, 3050-3054, 1995.
192. Reddy BS, Kawamori T, Lubet RA, Steele VE, Kelloff GJ, et al.: Chemopreventive efficacy of sulindac sulfone against colon cancer depends on time of administration during carcinogenic process. *Cancer Res*, 59, 3387-3391, 1999.
193. Hagiwara A, Miyashita K, Nakanishi T, Sano M, Tamano S, et al.: Pronounced inhibition by a natural anthocyanin, purple corn color, of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (phIP)-associated colorectal carcinogenesis in male f344 rats pretreated with 1,2-dimethylhydrazine. *Cancer Lett* 171, 17-25, 2001.
194. Furukawa K, Yamamoto I, Tanida N, Tsujiai T, Nishikawa M, The effects of dietary fiber from *Lagenaria scineraria* (yugao-melon) on colonic carcinogenesis in mice. *Cancer* 75, 1508-1515, 1995.
195. Piazza GA, Alberts DS, Hixson LJ, Paranka NS, Li H, et al.: Sulindac sulfone inhibits azoxymethane-induced colon carcinogenesis in rats without reducing prostaglandin levels. *Cancer Res*, 57: 2909-2915, 1997.
196. Craven PA, and Derubertis FR: Effects of Aspirin on 1,2-Dimethylhydrazine-Induced Colonic Carcinogenesis. *Carcinogenesis (Lond.)* 13, 541-546, 1992.
197. Tanaka T, Kojima T, Suzui M, and Mori H: Chemoprevention of colon carcinogenesis by the natural product of a simple phenolic compound protocatechuic acid: suppressing effects on tumor development and biomarkers expression on colon tumorigenesis. *Cancer Res*, 53, 3908-3913, 1993.
198. Earnest DL, Holubec H, Wali RK, Jolley CS, Bissonnette M, et al.: Chemoprevention of azoxymethane-induced colonic carcinogenesis by supplemental dietary ursodeoxycholic acid. *Cancer Res*, 54, 5071-5074, 1994.
199. Madar Z, Weiss O, Timar B, Gurevich P, and Zusman I: The effects of high-fiber diets on chemically induced colon cancer in rats. *Cancer J*, 9, 207-211, 1996.
200. Narisawa T, Fukaura Y, Tanida N, Hasebe M, Ito M, et al.: Chemopreventive efficacy of low dose of pravastatin, an HMG-coa reductase inhibitor, on 1,2-dimethylhydrazine-induced colon carcinogenesis in ICR mice. *Tohoku J. Exper. Med*, 180, 131-138, 1996.
201. Reddy BS, Tokumo K, Kulkarni N, Aligia C, and Kelloff G: Inhibition of colon carcinogenesis by prostaglandin synthesis inhibitors and related compounds. *Carcinogenesis (Lond.)* 13, 1019-1023, 1992.
202. Reddy BS, and Maruyama H: Effect of dietary fish oil on azoxymethane-induced colon carcinogenesis in male F344 rats. *Cancer Res*, 46, 3367-3370, 1986.
203. Wilpart M, Roberfroid M: Intestinal carcinogenesis and dietary fibers: the influence of cellulose or fybogel chronically given after exposure to DMH. *Nutr. Cancer* 10, 39-51, 1987.
204. McIntosh GH, Royle PJ, and Playne MJ: A probiotic strain of *Lactobacillus acidophilus* reduces DMH-induced large intestinal tumors in male Sprague-Dawley rats. *Nutr. Cancer* 35, 153-159, 1999.
205. Narisawa T, Fukaura Y, Hasebe M, Nomura S, Oshima S, et al.: Prevention of N-methylnitrosourea-induced colon carcinogenesis in F344 rats by lycopene and tomato juice rich in lycopene. *Jap. J. Cancer Res*, 89, 1003-1008, 1998.
206. Reddy BS, Hirose Y, Cohen LA, Simi B, Cooma I, et al.: Preventive potential of wheat bran fractions against experimental colon carcinogenesis: implications for human colon cancer prevention. *Cancer Res*, 60, 4792-4797, 2000.
207. Kawamori T, Tanaka T, Suzui M, Okamoto K, Tamai Y, et al.: Chemoprevention of azoxymethane-induced intestinal carcinogenesis by a novel synthesized retinoidal butenolide, 5-hydroxy-4-(2-phenyl-(e)ethenyl)-2(5h)-furanone, in rats. *Carcinogenesis (Lond.)* 16, 795-800, 1995.
208. Wattenberg LW: Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-Hydroxy-3,7,11-Trimethyl-1,6,10-Dodecatriene (Nerolidol). *Carcinogenesis (Lond.)* 12, 151-152, January 1991.
209. Tatsuta M, Iishi H, Baba M, Ichii M, Nakaizumi A, et al.: Inhibition by putrescine of experimental carcinogenesis in rat colon induced by azoxymethane. *Intl. J. Cancer* 47, 738-741, 1991.
201. Sumiyochi H, and Wargovich M.J: Chemoprevention of 12 Dimethylhydrazine induced colon cancer in mice by naturally occurring organosulfur compounds. *Cancer res* 50, 5084-5087, 1990.
211. Yoshimi N, Walaszek Z, Mori H, Hanausek M, Szemraj J, et al.: Inhibition of azoxymethane-induced rat colon carcinogenesis by potassium hydrogen d-glucarate. *Intl. J. Oncol.* 16, 43-48, 2000.
212. Corasanti JG, Hobika GH, and Markus G: Interference with dimethylhydrazine induction of colon tumors in mice by E-aminocaproic acid. *Science* 216, 1020-1021, 1982.
213. Bi S, Geng BQ, and Yong DG: Effects of menadione on 1,2-dimethylhydrazine-induced mouse colon adenocarcinoma. *Acta Pharmacologica Sinica* 14, 17-20, 1993.
214. Madar Z, Timar B, Nyska A, and Zusman I: Effects of high-fiber diets on pathological changes in DMH-induced rat colon cancer. *Nutr. Cancer* 20, 87-96, 1993.
215. Ohkami H, Tazawa K, Yamashita I, Shimizu T, Murai K, et al.: Effects of apple pectin on fecal bacterial enzymes in azoxymethane-induced rat colon carcinogenesis. *Jap. J. Cancer Res*, 86, 523-529, 1995.
216. Rao CV, Rivenson A, Simi B, Zang E, Kelloff G, et al.: Chemoprevention of colon carcinogenesis by sulindac, a nonsteroidal anti-inflammatory agent. *Cancer Res*, 55, 1464-1472, 1995.
217. Dillehay DL, Webb SK, Schmelz EM, and Merrill AH: Dietary sphingomyelin inhibits 1,2-dimethylhydrazine-induced colon cancer in CFI mice. *J. Nutr*, 124, 615-620, 1994.
218. Reddy BS, Rivenson A, Kulkarni N, Upadhyaya P, and ElBayoumy K: Chemoprevention of colon carcinogenesis by the synthetic organoselenium compound 1,4-phenylenebis(methylene)selenocyanate. *Cancer Res*, 52, 5635-5640, 1992.
219. Wargovich MJ, Allnut D, Palmer C, Anaya P, and Stephens LC: Inhibition of the promotional phase of azoxymethane induced colon carcinogenesis in the F344 rat by calcium lactate: effect of simulating 2 human nutrient density levels. *Cancer Lett*, 53, 17-25, 1990.
220. Nayini JR, Sugie S, Elbayoumy K, Rao CV, Rigotty J, et al.: Effect of dietary benzylselenocyanate on azoxymethane-induced colon carcinogenesis in male F344 rats. *Nutr. Cancer* 15, 129-139, 1991.
221. Zusman I: Comparative anticancer effects of vaccination and dietary factors on experimentally-induced cancers. *In Vivo* 12, 675-690, 1998.
222. Hughes JS, Ganthavorn C, and Wilsonsanders S: Dry beans inhibit azoxymethane-induced colon carcinogenesis in F344 rats. *J. Nutr*, 127, 2328-2333, 1997.
223. Ullah A, and Shamsuddin AM: Dose dependent inhibition of large intestinal cancer by inositol hexaphosphate in F344 rats. *Carcinogenesis (Lond.)* 11, 2219-2222: 1990.
224. Narisawa T, Fukaura Y, Yazawa K, Ishikawa C, Isoda Y, et al.: Colon cancer prevention with a small amount of dietary perilla oil high in alpha-linolenic acid in an animal model. *Cancer* 73, 2069-2075, 1994.
225. Minoura T, Takata T, Yamamoto M, et al.: Effect of dietary eicosapentaenoic acid on azoxymethane induced colon carcinogenesis in rats.

- Cancer Res, 48, 4790-4794, 1988.
226. Tatsuta M, Iishi H, Baba M, Uehara H, and Nakaizumi A: Chemoprevention by amiloride of experimental carcinogenesis in rat colon induced by azoxymethane. *Carcinogenesis (Lond.)* 16, 941-942, 1995.
227. Yamane T, Hagiwara N, Tateishi M, Akachi S, Kim M, et al.: Inhibition of azoxymethane-induced colon carcinogenesis in rat by green tea polyphenol fraction. *Jap. J. Cancer Res*, 82, 1336-1339, 1991.
228. Fukutake M, Nakatsugi S, Isoi T, Takahashi M, Ohta T, et al.: Suppressive effects of nimesulide, a selective inhibitor of cyclooxygenase-2, on azoxymethane-induced colon carcinogenesis in mice. *Carcinogenesis (Lond.)* 19, 1939-1942, 1998.
229. Tanaka T, Kohno H, Murakami M, Shimada R, Kagami S, et al.: Suppression of azoxymethane-induced colon carcinogenesis in male F344 rats by mandarin juices rich in beta-cryptoxanthin and hesperidin. *Intl. J. Cancer* 88, 146-150, 2000.
230. Reddy BS, Rivenson A, ElBayoumy K, Upadhyaya P, Pittman B, et al.: Chemoprevention of colon cancer by organoselenium compounds and impact of high- or low-fat diets. *J. Natl. Cancer Inst*, 89, 506-512, 1997.
231. Goldin BR, and Gorbach SL: Effect of *Lactobacillus acidophilus* dietary supplements on 1,2-dimethylhydrazine dihydrochloride-induced intestinal cancer in rats. *J. Natl. Cancer Inst*, 64, 263-265, 1980.
232. Narisawa T, Fukaura Y, Terada K, and Sekiguchi H: Prevention of N-methylnitrosourea-induced colon tumorigenesis by ursodeoxycholic acid in F344 rats. *Jap. J. Cancer Res*, 89, 1009-1013, October 1998.
233. Zoran DL, Turner ND, Taddeo SS, Chapkin RS, and Lupton JR: Wheat bran diet reduces tumor incidence in a rat model of colon cancer independent of effects on distal luminal butyrate concentrations. *J. Nutr*, 127, 2217-2225, 1997.
234. Hakkak R, Korourian S, Ronis MJ J, Johnston, JM, Badger TM: Dietary whey protein protects against azoxymethane-induced colon tumors in male rats. *Cancer Epidemiol Biomarkers Prev* 10, 555-558, 2001.
235. Rao CV, Desai D, Rivenson A, Simi B, Amin S, et al.: Chemoprevention of colon carcinogenesis by phenylethyl-3-methylcaffeate. *Cancer Res*, 55, 2310-2315, 1995.
236. Reddy BS, Rao CV, Rivenson A, and Kelloff G: Chemoprevention of colon carcinogenesis by organosulfur compounds. *Cancer Res*, 53, 3493-3498, 1993.
237. Sinkeldam EJ, Kuper CF, Bosland MC, Hollanders VMH, and Vedder DM: Interactive effects of dietary wheat bran and lard on N-methyl-N'-nitro-N-nitrosoguanidine induced colon carcinogenesis in rats. *Cancer Res*, 50, 1092-1096, 1990.
238. Karkare MR, Clark TD, and Glauert HP: Effect of Dietary Calcium on Colon Carcinogenesis Induced by a Single Injection of 1,2-Dimethylhydrazine in Rats. *J. Nutr*, 121, 568-577, April 1991.
239. McIntosh GH, Regester GO, Leleu RK, Royle PJ, and Smithers GW: Dairy proteins protect against dimethylhydrazine-induced intestinal cancers in rats. *J. Nutr*, 125, 809-816, 1995.
240. Reddy BS, Sugie S, Maruyama H, and Marra P: Effect of dietary excess of inorganic selenium during initiation and postinitiation phases of colon carcinogenesis in F344 rats. *Cancer Res*, 48, 1777-1780, 1988.
241. Anisimov VN, Zabezhinski MA, Popovich IG, Berstein LM, Kovalenko IG, et al.: Prevention of spontaneous and chemically induced carcinogenesis using activated carbon fiber adsorbent. III. inhibitory effect of the activated carbon fiber adsorbent 'aqualen' on 1,2-dimethylhydrazine-induced intestinal carcinogenesis in rats. *Cancer Lett* 138, 27-35, 1999.
242. Caderni G, Defilippo C, Lucheri C, Salvadori M, Giannini A, et al.: Effects of black tea, green tea and wine extracts on intestinal carcinogenesis induced by azoxymethane in F344 rats. *Carcinogenesis (Lond.)* 21, 1965-1969, 2000.
243. Rao CV, Rivenson A, Simi B, and Reddy BS: Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. *Cancer Res*, 55, 259-266, 1995.
244. Holt PR, Mokuolu AO, Distler P, Liu T, and Reddy BS: Regional distribution of carcinogen-induced colonic neoplasia in the rat. *Nutr. Cancer* 25, 129-135, 1996.
245. Rao CV, Rivenson A, Katiwalla M, Kelloff GJ, and Reddy BS: Chemopreventive effect of oltipraz during different stages of experimental colon carcinogenesis induced by azoxymethane in male F344 rats. *Cancer Res*, 53, 2502-2506, 1993.
246. Reddy BS, Rao CV, Rivenson A, and Kelloff G: Inhibitory effect of aspirin on azoxymethane-induced colon carcinogenesis in F344 rats. *Carcinogenesis (Lond.)* 14, 1493-1497, 1993.
247. Beaty MM, Lee EY, and Glauert HP: Influence of dietary calcium and vitamin-d on colon epithelial cell proliferation and 1,2-dimethylhydrazine-induced colon carcinogenesis in rats fed high fat diets. *J. Nutr*, 123, 144-152, 1993.
248. Raicht RF, Cohen BI, Fazzini EP, Sarwal AN, and Takahashi M: Protective effect of plant sterols against chemically induced colon tumors in rats. *Cancer Res*, 40, 403-5, 1980.
249. Lindner MA: A fish oil diet inhibits colon cancer in mice. *Nutr. Cancer* 15, 1-11, 1991.
250. Reddy BS, Sugie S, Maruyama H, ElBayoumy K, and Marra P: Chemoprevention of colon carcinogenesis by dietary organoselenium, benzylselenocyanate, in F344 rats. *Cancer Res*, 47, 5901-5904, 1987.
251. Reddy BS, Sugie S, and Lowenfels A: Effect of voluntary exercise on azoxymethane-induced colon carcinogenesis in male F344 rats. *Cancer Res*, 48, 7079-7081, 1988.
252. Reddy BS, Narisawa T, and Weisburger JH: Effect of a diet with high levels of protein and fat on colon carcinogenesis in F344 rats treated with 1,2-dimethylhydrazine. *J. Natl. Cancer Inst*, 57, 567-569, 1976.
253. Rao CV, Wang CQ, Simi B, Rodriguez JG, Cooma I, et al.: Chemoprevention of colon cancer by a glutathione conjugate of 1,4-phenylenebis(methylene)selenocyanate, a novel organoselenium compound with low toxicity. *Cancer Res*, 61, 3647-3652, 2001.
254. Kumar SP, Roy SJ, Tokumo K, and Reddy BS: Effect of different levels of caloric restriction on azoxymethane induced colon carcinogenesis in male F344 rats. *Cancer Res*, 50, 5761-5766, 1990.
255. Huang MT, Lou YR, Ma W, Newmark HL, Reuhl KR, et al.: Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice. *Cancer Res*, 54, 5841-5847, 1994.
256. Tsukamura M, Goto H, Arisawa T, Hayakawa T, Nakai N, et al.: Dietary maltitol decreases the incidence of 1,2-dimethylhydrazine-induced cecum and proximal colon tumors in rats. *J. Nutr*, 128, 536-540, 1998.
257. Tanaka T, Makita H, Ino N, Rahman W, Mori H, et al.: Modifying effects of the arotinoid mofarotene (ro 40-8757) on azoxymethane-induced rat colon and liver carcinogenesis. *Cancer J* 9, 260-268, 1996.
258. Nyce JW, Magee PN, Hard GC, and Schwartz A: Inhibition of 1,2-dimethylhydrazine-induced colon tumorigenesis in Balb/c mice by dehydroepiandrosterone. *Carcinogenesis (Lond.)* 5, 57-62, 1984.
259. Penman ID, Elomar E, McGregor JR, Hillan KJ, Odwyer PJ, et al.: Omeprazole inhibits colorectal carcinogenesis induced by azoxymethane in rats. *Gut* 34, 1559-1565, 1993.
260. VinasSalas J, BiendichoPalau P, PinolFelis C, MiguelsanzGarcia S, and PerezHolanda S: Calcium inhibits colon carcinogenesis in an experimental model in the rat. *Europ. J. Cancer* 34, 1941-1945, 1998.
261. Anisimov VN, Popovich IG, and Zabezhinski MA: Melatonin and colon carcinogenesis. I. inhibitory effect of melatonin on development of intestinal tumors induced by 1,2-dimethylhydrazine in rats. *Carcinogenesis (Lond.)* 18, 1549-1553, 1997.
262. Tanaka T, Kawabata K, Kakumoto M, Makita H, Ushida J, et al.: Modifying effects of a flavonoid morin on azoxymethane-induced large bowel tumorigenesis in rats. *Carcinogenesis (Lond.)* 20, 1477-1484, 1999.
263. Sekine K, Watanabe E, Nakamura J, Takasuka N, Kim DJ, et al.: Inhibition of azoxymethane-initiated colon tumor by bovine lactoferrin administration in F344 rats. *Jap. J. Cancer Res*, 88, 523-526, 1997.
264. Reddy BS, and Sugie S: Effect of different levels of omega-3 and omega-6 fatty acids on azoxymethane-induced colon carcinogenesis in F344 rats. *Cancer Res*, 48, 6642-6647, 1988.
265. Rijnkels JM, Hollanders VMH, Woutersen RA, Koeman JH, and Alink GM: Interaction of dietary fat and of a vegetables/fruit mixture on 1,2-dimethylhydrazine- or n-methyl-n'-nitro-n-nitrosoguanidine-induced colorectal cancer in rats. *Cancer Lett*, 114, 297-298, 1997.
266. Singh J, Rivenson A, Tomita M, Shimamura S, Ishibashi N, et al.: *Bifidobacterium longum*, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulates the intermediate biomarkers of colon carcinogenesis. *Carcinogenesis (Lond.)* 18, 833-841, 1997.
267. Billings PC, Newberne PM, and Kennedy AR: Protease inhibitor suppression of colon and anal gland carcinogenesis induced by dimethylhydrazine. *Carcinogenesis (Lond.)* 11, 1083-1086, 1990.
268. Thorling EB, Jacobsen NO, and Overvad K: The effect of treadmill exercise on azoxymethane-induced intestinal neoplasia in the male fischer rat on two different high-fat diets. *Nutr. Cancer* 22, 31-41, 1994.
269. Kawaura A, Takahashi A, Tanida N, Oda M, and Shimoyama T: 1-alpha-hydroxyvitamin D3 suppresses colonic tumorigenesis induced by repetitive intrarectal injection of N-methyl-N-nitrosourea in rats. *Cancer Lett*, 55, 149-152, 1990.
270. Heitman DW, Hardman WE, and Cameron IL: Dietary Supplementation with Pectin and Guar Gum on 1,2-Dimethylhydrazine-Induced Colon Carcinogenesis in Rats. *Carcinogenesis (Lond.)* 13, 815-818, 1992.
271. Narisawa T, Fukaura Y, Oshima S, Inakuma T, Yano M, et al.:

- Chemoprevention by the oxygenated carotenoid beta-cryptoxanthin of n-methylnitrosourea-induced colon carcinogenesis in F344 rats. *J. Cancer Res*, 90, 1061-1065, 1999.
272. Goldin BR, Gualtieri LJ, and Moore RP: The effect of lactobacillus GG on the initiation and promotion of DMH-induced intestinal tumors in the rat. *Nutr. Cancer* 25, 197-204, 1996.
273. Reddy BS, Wang CX, Samaha H, Lubet R, Steele VE, et al.: Chemoprevention of colon carcinogenesis by dietary perillyl alcohol. *Cancer Res*, 57, 420-425, 1997.
274. Yamamoto I, Maruyama H, and Moriguchi M: Effect of beta-carotene, sodium ascorbate and cellulose on 1,2-dimethylhydrazine-induced intestinal carcinogenesis in rats. *Cancer Lett*, 86, 5-9 1994.
275. Balansky R, Gyosheva B, Ganchev G, Mircheva Z, Minkova S, et al.: Inhibitory effects of freeze-dried milk fermented by selected *Lactobacillus bulgaricus* strains on carcinogenesis induced by 1,2-dimethylhydrazine in rats and by diethylnitrosamine in hamsters. *Cancer Lett*, 147, 125-137, 1999.
276. Sugie S, Okamoto K, Rahman KMW, Tanaka T, Kawai K, et al.: Inhibitory effects of plumbagin and juglone on azoxymethane-induced intestinal carcinogenesis in rats. *Cancer Lett*, 127, 177-183, 1998.
277. McIntosh GH, Royle PJ, and Pointing G: Wheat aleurone flour increases cecal beta-glucuronidase activity and butyrate concentration and reduces colon adenoma burden in azoxymethane-treated rats. *J. Nutr*, 131, 127-131, 2001.
278. Kawamori T, Lubet R, Steele VE, Kelloff GJ, Kaskey RB, et al.: Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. *Cancer Res*, 59, 597-601, 1999.
279. Seril DN, Liao J, Ho KKL, Yang CS, and Yang GY: Inhibition of Chronic Ulcerative Colitis (UC)-Associated Carcinogenesis in Mice by N-Acetyl-L-Cysteine (NAC): Effects on Oxidative/Nitrosative Damage and Proliferation - Proc. Am. Assoc. Cancer Res, 42, #4647 (abstr), 2001.
280. Miyagi Y, Om AS, Chee KM, and Bennink MR: Inhibition of azoxymethane-induced colon cancer by orange juice. *Nutr. Cancer* 36, 224-229, 2000.
281. Chang WCL, Chapkin RS, and Lupton JR: Predictive value of proliferation, differentiation and apoptosis as intermediate markers for colon tumorigenesis. *Carcinogenesis (Lond.)* 18, 721-730, 1997.
282. Leleu RK, Young GP, and McIntosh GH: Folate deficiency reduces the development of colorectal cancer in rats. *Carcinogenesis (Lond.)* 21, 2261-2265, 2000.
283. Pence BC, Dunn DM, Zhao C, Landers M, and Wargovich MJ: Chemopreventive effects of calcium but not aspirin supplementation in cholic acid-promoted colon carcinogenesis: correlation with intermediate endpoints. *Carcinogenesis (Lond.)* 16, 757-765, 1995.
284. Sugie S, Okamoto K, Okumura A, Tanaka T, and Mori H: Inhibitory effects of benzyl thiocyanate and benzyl isothiocyanate on methylazoxymethanol acetate-induced intestinal carcinogenesis in rats. *Carcinogenesis (Lond.)* 15, 1555-1560, 1994.
285. Reddy BS, Kawamori T, Lubet R, Steele V, Kelloff G, et al.: Chemopreventive effect of s-methylmethane thiosulfonate and sulindac administered together during the promotion/progression stages of colon carcinogenesis. *Carcinogenesis (Lond.)* 20, 1645-1648, 1999.
286. Alink GM, Kuiper HA, Hollanders VMH, and Koeman JH: Effect of heat processing and of vegetables and fruit in human diets on 1,2-dimethylhydrazine-induced colon carcinogenesis in rats. *Carcinogenesis (Lond.)* 14, 519-524, 1993.
287. Mokady E, Schwartz B, Shany S, and Lamprecht SA: A protective role of dietary vitamin D3 in rat colon carcinogenesis. *Nutr. Cancer* 38, 65-73, 2000.
288. Takahashi T, Satou M, Watanabe N, Sakaitani Y, Takagi A, et al.: Inhibitory effect of microfibril wheat bran on azoxymethane-induced colon carcinogenesis in CF1 mice. *Cancer Lett* 141, 139-146, 1999.
289. Belleli A, Levy J, Guberman R, and Lamprecht SA: A protective role of 1,25-dihydroxyvitamin d3 in chemically induced rat colon carcinogenesis. *Carcinogenesis (Lond.)* 13, 2293-2298, 1992.
290. Bull A, Bird RP, Bruce WR, Nigro N, and Medline A: Effect of calcium on azoxymethane induced intestinal tumors in rats. *Gastroenterology*, 92, abstract #1332 (abstr), 1987.
291. Samelson SL, Nelson RL, and Nyhus LM: Protective role of faecal pH in experimental colon carcinogenesis. *J. Royal Soc. Med*, 78, 230-233, 1985.
292. Caderni G, Luceri C, Defilippo C, Salvadori M, Giannini A, et al.: Slow-release pellets of sodium butyrate do not modify azoxymethane (AOM)-induced intestinal carcinogenesis in F344 rats. *Carcinogenesis (Lond.)*, 22, 525-527, 2001.
293. Caderni G, Giannini A, Lancioni L, Luceri C, Biggeri A, et al.: Characterisation of aberrant crypt foci in carcinogen-treated rats: association with intestinal carcinogenesis. *Brit. J. Cancer* 71, 763-769, 1995.
294. Zhang XM, Stamp D, Minkin S, Medline A, Corpet DE, et al.: Promotion of aberrant crypt foci and cancer in rat colon by thermolyzed protein. *J. Natl Cancer Inst*, 84, 1026-1030, 1992.
295. Bruce WR, Giacca A, and Medline A: Possible mechanisms relating diet and risk of colon cancer. *Cancer Epidemiol. Biomark. Prev*, 9, 1271-1279, 2000.
296. Kelloff GJ, Boone CW, Steele VE, et al.: Mechanistic considerations in the evaluation of chemopreventive data. *Principles of Chemoprevention*. Stewart B.W, McGregor D, Kleihues P. eds. IARC Scientific Publications, 139, 203-214, 1996.
297. Angres G, and Beth M: Effects of dietary constituents on carcinogenesis in different tumor models: an overview from 1975 to 1988. in *Cancer and Nutrition*, Alfin-Slater RB, and Kritchevsky D. editors. Plenum Press, NY, 337-485, 1991.
298. Zhao LP, Kushi LH, Klein RD, and Prentice RL: Quantitative review of studies of dietary fat and rat colon carcinoma. *Nutr. Cancer*, 15, 169-177, 1991.
299. Schleiffer R, Duranton B, Gosse F, Bergmann C, and Raul F: Nitric oxide synthase inhibition promotes carcinogen-induced preneoplastic changes in the colon of rats. *Nitric Oxide - Biol. Chem*, 4, 583-589, 2000.
300. Jacoby RF, Seibert K, Cole CE, Kelloff G, and Lubet RA: The cyclooxygenase-2 inhibitor celecoxib is a potent preventive and therapeutic agent in the Min mouse model of adenomatous polyposis. *Cancer Res*. 60, 5040-5044, 2000.
301. Jacoby RF, Cole CE, Lubet RA, and You M: Effect of the nonspecific Cox1/2 inhibitor piroxicam and the ornithine decarboxylase inhibitor difluoromethylornithine (DFMO) on development of intestinal tumors in mice bearing germline alteration the the Msh2 or APC genes. *Proc. Am. Assoc. Cancer Res*. 42, #1422 (abstr), 2001.
302. Yang K, Fan K, Shinozaki H, Newmark H, Edelman W, et al.: Sulindac increases carcinoma development in the colons of mice with *Apc* mutations. *Proc. Am. Assoc. Cancer Res*. 40, #3488 (abstr), 1999.
303. Yang K, Fan K, Lia M, Edelman W, Augenlicht LH, et al.: Sulindac Increases Tumor Development in the Colon of Mice with *Mlh1 +/-* Mutation. *Proc. Am. Assoc. Cancer Res*. 42, #1423 (abstr), 2001.
304. Erdman SH, Ignatenko NA, Powell MB, Blohmmangone KA, Holubec H, et al.: APC-dependent changes in expression of genes influencing polyamine metabolism, and consequences for gastrointestinal carcinogenesis, in the Min mouse. *Carcinogenesis (Lond.)* 20, 1709-1713, 1999.
305. Takaku K, Sonoshita M, Sasaki N, Uozumi N, Doi Y, et al.: Suppression of intestinal polyposis in *Apc(delta 716)* knockout mice by an additional mutation in the cytosolic phospholipase A(2) gene. *J. Biol. Chem*, 275, 34013-34016, 2000.
306. Steele VA, Wargovich MJ, Pereira MA, Rao CV, Lubet RA, et al.: Comparison of the azoxymethane AOM-induced rat colon crypt assay with the rat colon tumor assay for cancer chemopreventive agents. *Proc. Am. Assoc. Cancer Res*, 40, 57 (#A377) (abstr), 1999.
307. Carter JW, Lancaster HK, Hardman WE, and Cameron IL: Distribution of intestine-associated lymphoid tissue, aberrant crypt foci, and tumors in the large bowel of 1,2-dimethylhydrazine-treated mice. *Cancer Res*, 54, 4304-4307, 1994.
308. Paulsen JE, Namork E, Steffensen IL, Eide TJ, and Alexander J: Identification and quantification of aberrant crypt foci in the colon of min mice - a murine model of familial adenomatous polyposis. *Scand. J. Gastroenterol* 35, 534-539, 2000.
309. Pretlow TP, Bird RP: Correspondence re: Y. Yamada et al., Frequent beta-catenin gene mutations and accumulations of the protein in the putative preneoplastic lesions lacking macroscopic aberrant crypt foci appearance, in rat colon carcinogenesis. *Cancer Res* 60: 3323-3327, 2000; and Sequential analysis of morphological and biological properties of beta-catenin-accumulated crypts, provable premalignant lesions independent of aberrant crypt foci in rat colon carcinogenesis. *Cancer Res* 61: 1874-1878, 2001. *Cancer Res* 61, 7699-7700, 2001.

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 Durant 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 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 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 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 lactate 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
<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.