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# DIET AND EXPERIMENTAL COLORECTAL CANCER

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## ABSTRACT

National and international geographic variations in the incidence and mortality rates of colorectal cancer along with changes in prevalence among migrant populations would suggest that environmental factors have a role in the aetiology of this disease. Animal models of chemically induced colonic carcinogenesis have been widely used to assess the effect of dietary components such as fat and fibre. These studies have shown that the type of fat is important. Polyunsaturated vegetable oils rich in ω-6 fatty acids have a promotional role whereas fish oil rich in ω–3 fatty acids has no promotional effect and may even inhibit tumour formation. Studies of the effect of fibres have shown that insoluble dietary fibres such as wheat bran and cellulose may have a protective role. However, soluble fibres such as pectin and psyllium offer little protection and in fact carrageenan may have a promotional effect. It has been suggested that phytic acid (inosital hexaphosphate), a component of many fibre-rich diets, rather than fibre per se, has a role in the suppression of colonic carcinogenesis. Despite conflicting evidence, it may be plausible to advocate a high fibre, low fat diet as a measure of secondary prevention of colorectal cancer.

Key words: Colorectal cancer, Fat, Fibre, DMH, AOM, MAM

## INTRODUCTION

Colorectal carcinoma is the second most common cause of cancer death in western industrialised countries. Epidemiological data and migration studies have strongly indicated that dietary factors such as the abundance of fat and/or deficiency in fibre, play a major role in its aetiology (1,2). Animal models of chemically induced colon cancer have provided more detailed information about pathogenesis, development, and modulation of this disease. Enhancement and suppression of experimental colonic carcinogenesis by dietary supplementation contributes to a better understanding of the mechanism of cancer formation and modulation. Dimethylhydrazine (DMH) and its metabolites, azoxymethane (AOM) and methylazoxymethanol (MAM) have been used extensively to study colon cancer in susceptible animals. This review will focus on the effect of dietary fat and fibre in experimental colon cancer induced by DMH and its metabolites in rodents.

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## DIETARY FAT AND COLON CANCER

The excessive ingestion of dietary fat has been linked with the development of colonic cancer (2). It is important to look closely at the types of fat being consumed rather than total fat consumption. It is difficult to investigate the effect of fat or types of fat in human diets as interactions with other nutritional factors can led to misinterpretation of results. Many workers use animal models, in which other factors may be controlled, to test the hypothesis that the quantity and quality of dietary fat modulates colon carcinogenesis. Evidence from animal studies would suggest that vegetable oils rich in polyunsaturated omega-6 (ω-6) fatty acid promote colon carcinogenesis more effectively than saturated fats, while fish oil rich in polyunsaturated omega-3 (ω-3) fatty acid may inhibit carcinogenesis. Omega-3 and omega-6 fatty acids are essential fatty acids and must be obtained from the diet. It is necessary to distinguish these two classes of fatty acids as they have different metabolic and physiological functions.

### Polyunsaturated Fatty Acids

**Omega-6 fatty acid:** Corn and safflower oil rich in ω-6 fatty acid have been shown to promote the development of colon cancer. Animals fed on a diet containing 20% corn oil or 20% safflower oil are more susceptible to DMH induced colon tumours and excrete higher levels of biliary bile acids, faecal bile acids and neutral sterols when compared to rats fed Purina Lab Chow which contains approximately 4.5% fat (3). If the concentration of corn oil in the diet is reduced to 5% there is a lower incidence of colon tumours (4). The ability of corn oil to promote the development of colon tumours depends not only on the concentration in the diet but also on the time of feeding. High levels of corn oil have been shown to enhance tumour incidence and multiplicity of AOM-induced carcinogenesis in F344 rats when fed during postinitiation stage *i.e.* after 2 weekly injections of carcinogen (3,5). However, the same diet fed during initiation had no effect (5).

In contrast, Nauss et al. (6) found no significant effect of high corn oil diet on tumour incidence, latency, size, frequency or histological classification in DMH-treated rats. They explained this view by differences in the route of carcinogen administration and genetic differences between strains of rats. They repeated this work (7) using Sprague Dawley (SD) rats treated with DMH by gavage or subcutaneous injection and fed either 5% or 24% corn oil diet. Again, they could show no significant effect suggesting that dietary variables other than fat may affect susceptibility to colon carcinogenesis.

Increased levels of dietary fats have been shown to promote DMH absorption (8), and toxicity to colonic epithelial cells (9). Nuclear aberrations of colon mucosa were found to be significantly increased 24 hours after DMH treatment in animals fed on a diet containing 20% corn oil compared to animals fed on low fat diets. Suppression of lymphocyte response to concanavalin A (Con A) and phytohaemagglutinin-M (PHA) along with T-cell cytotoxicity against colon tumour cell targets has been associated with corn oil (10) and safflower oil consumption (11). DMH alone does not influence lymphocyte response. The splenic natural killer (NK) cell cytotoxicity was not significantly affected by dietary fat, carcinogen treatment, or tumour development (12). Increased colonic crypt cell proliferation in animals fed on high fat diet may be an important factor in experimental carcinogenesis (13). However, conflicting evidence (14) shows that after 10 and 21 weeks a high corn oil-diet has no effect on indices of colonic cell proliferation in the distal colon, while at 34 weeks, tumour incidence was greater and colonic cell labelling indices were lower. In addition, a high corn oil diet alone did not produce hyperproliferation and hyperplasia in either female rats or mice compared with low corn oil diet (15). This would suggest that the effect of fat on tumour incidence is not associated with kinetic changes in the distal colon.

Increased tumour induction by high dietary fat fed during the postinitiation stage has been associated with increased luminal bile acids and increased activity of colonic mucosal ornithine

decarboxylase (ODC). It has been suggested that increased ODC activity may be an important component in the mechanism of fat induced tumour promotion (16).

Interactions between fat and other dietary supplementations have been reported. When corn oil is combined with milk the tumour enhancing effects are evident but not when combined with the milk protein casein (10). Tumour incidence and frequency were significantly increased in rats fed on diets high in fat and low in vitamin A when compared to those fed on high fat with normal vitamin A diets (17). However, if the level of vitamin A is raised above 10 mg/g no further beneficial effect is noted. The addition of calcium to a high fat diet has been demonstrated to inhibit colon carcinogenesis (18). Trudel et al. (19) studied the effect of a polyunsaturated (safflower oil) and a saturated (lard oil) fat diet on DMH-induced carcinogenesis with or without purified fibre (cellulose) and demonstrated a positive correlation between high total dietary fat intake and the incidence and number of tumours per animal. Although no difference between polyunsaturated and saturated fats could be observed, they postulated a higher low-grade promoting effect by polyunsaturated fat according to the addition of cellulose to the high-fat diet provided a partial (safflower) and a complete (lard) protection against the deleterious effect of fat.

**Omega-3 fatty acid:** Several studies have shown that dietary supplementation with ω-3 fatty acid decreases the number and size of tumours and increases the time elapsed before appearance of tumours of the breast, pancreas and colon in animals (20). Evidence from epidemiological and clinical studies suggests that a high consumption of fish oil may protect against colorectal cancer.

Reddy and Maruyama (16) demonstrated that a dietary intake of 22.5% menhaden fish oil with 1% corn oil significantly inhibited AOM induced colon tumours when compared to a 23.5% corn-oil diet and had an inhibitory effect on the colonic concentration of secondary bile acids. The effect of various concentrations of dietary menhaden fish oil on tumour production suggests that inhibition of colon tumours is not dose-dependent, whereas the inhibition of ODC activity in the colonic mucosa is (21). ODC activity has been shown to be significantly lower in animals fed perilla oil. The ODC induction and inhibition alone is not sufficient for colon tumour promotion and inhibition respectively though colonic mucosal ODC activity increases in rats fed high fat diet (16). The reduced incidence and multiplicity of colon adenocarcinomas in animals fed high fish-oil diet were noticed at both initiation and post initiation stages of carcinogenesis (5). Omega-3 fatty acid was highest in plasma and colon mucosa cells of mice fed fish oil diet and showed negative association with tumours (22). Deschner et al. (23) showed that a ratio of ω-3 to ω-6 fatty acids of approximately 1.0 prevented the development of an adenoma-type proliferative pattern, thereby reducing focal dysplasia and subsequent tumour incidence in AOM-treated mice. Intragastric gavage of purified docosahexaenoic acid suppressed the formation and growth of aberrant crypt foci induced by DMH in rats (24).

In the absence of DMH, fish oil and corn oil equally augmented protein kinase C (PKC) activity and decreased the ratio of soluble/particulate PKC (25). With DMH treatment, however, fish oil supplementation resulted in a pattern of PKC activity and distribution more typical of a low fat diet, particularly when fish oil diet preceded DMH treatment. The liver microsomal metabolism of carcinogens affected by dietary fats including fish oil has been reported (26).

It has been shown that ω-3 fatty acids inhibit oxidative metabolism of arachidonic acid by the cyclooxygenase pathway involved in prostaglandin synthesis (27) and subsequently decreases prostaglandin E2 (PGE2) production. Recent studies have shown that indomethacin, an inhibitor of prostaglandin synthesis, inhibits colon carcinogenesis. Minoura et al. (28) reported that a diet containing 4.7% eicosopentaenoic acid (EPA, ω-3 fatty acid) significantly lowered the tumour incidence and tumour yields compared to a linoleic acid (ω-6 fatty acid) diet. In spite of the higher arachidonic acid content, the EPA diet suppressed the excessive production of PGE2 (28) and menhaden oil diet increased lipid peroxidation (29) in colon tumours.

**Monounsaturated Fatty Acids**

Olive oil contains a preponderance of monounsaturated fat high in oleic acid (C18:1). A high-olive oil diet markedly reduces the faecal excretion of cholesterol and significantly inhibits the colon tumour incidence compared to diets containing high level of ω-6 fatty acid (3). Furthermore, a significant increase in the excretion of primary bile acids (cholic acid and chenodeoxycholic acid) but not secondary bile acids (deoxycholic and lithocholic acid) was observed in rats fed high-olive oil diets suggesting a decrease in the microbial modification of primary bile acids in the gut. Earlier studies showed that monounsaturated fatty acid had a neutral influence on blood cholesterol concentration (30), which might be related to colon tumour formation. A recent investigation has suggested that blood cholesterol concentration falls after consumption of a diet rich in olive oil (31). The effects of a high olive oil diet needs further investigation, since low serum cholesterol levels appear to indicate a greater risk for colon cancer.

**Saturated Fatty Acids**

**Coconut oil:** Broitman (11) reported that a 20% coconut oil diet enhanced the incidence and number of DMH-induced colon cancers in male SD rats compared to 5% coconut diet. However, there was a 16% reduction of total caloric intake in the rats fed a 5% coconut diet making it difficult to determine if this effect was due to reduced fat consumption or restricted caloric intake. The number of colonic tumours induced by DMH in rats fed a high coconut diet is less than those fed high safflower oil diet, suggesting that a polyunsaturated fat diet is more effective in promoting carcinogenesis. This effect was associated with a decrease in serum cholesterol levels concomitant with an increase in faecal bile acids (11) and suppression of lymphocyte response to PHA in polyunsaturated fat-fed animals. When diet containing high coconut oil was given during postinitiation period, no promoting effect on tumour incidence and decreased concentration of faecal deoxycholic acid and total bile acids have been noted in AOM-induced carcinogenesis (3). Salim (32) showed that the incidence of colonic cancer was directly dependent on dietary fat intake and that colonic carcinogens were less harmful when a low-fat diet was consumed. A dose-dependent protection against the promoting effect of high-fat diet by administration of radical scavengers suggests that oxygen-derived free radicals play an important permissive role in development of colon cancer.

**Animal fat (Beef & Lard):** Animals fed high beef fat diet ate less food and developed more and larger intestinal tumours with more metastases to the abdominal cavity, lungs, and liver (33). They suggested that the carcinogenic enhancement was due to nutritional deficiencies in the diet and/or alterations in luminal bile acid content, since a significant increase in faecal deoxycholic acid level and cholic acid degradation was found in animals fed on high fat diet over animals fed normal diets. Another study demonstrated increased intestinal tumour frequency when a high-beef fat diet was given after, but not during or before, the administration of carcinogen (34). This increase occurred even after a prolonged interval (10 weeks) between the last AOM injection and high fat consumption.

Animals fed a high beef hamburger diet were more susceptible to DMH induced colonic tumours with an emphasis on production of adenocarcinomas compared with rats fed low beef hamburger diet although the incidence was not statistically significant (4). Furthermore, male F344 rats fed a semipurified diet containing 20% beef fat and treated with DMH or MAM had a greater incidence of colon tumours than rats fed a diet containing 5% beef fat (35). The type of fat made no difference in promoting carcinogenesis at the 20% level (36).

It has also been reported (37) that animals fed 20% beef-fat diet after post initiation period (one week after 2 weekly AOM-injection) had a greater incidence of large bowel tumours than animals fed 5% beef fat diet. High beef fat with low fibre diet led to the greatest risk for macroscopic

tumour production and the low fat with high fibre diet to the lowest risk in AOM-induced carcinogenesis (38). The increased incidence and frequency of colonic tumours were associated with a higher total concentration of free faecal bile acids and more marked surface architectural change of crypt cells (39) in animals fed high beef fat and low fibre . A greater mean number and larger mean size of foci of aberrant crypts, which are potential precursor lesions of chemically induced colon tumour, had been found in mice fed high beef diet compared to animals fed low-fat diet (40).

In most studies of high dietary beef fat, however, no effect on chemically induced colon tumour incidence and multiplicity has been shown. The increased colon tumour incidence was only noticed when SD rats were fed high-beef fat diet with 2% corn oil (41), suggesting that essential fatty acids are required for DMH-induced intestinal carcinogenesis. Since DMH-treated SD rats fed 30% beef fat for 50 weeks had a significantly increased cumulative probability of death due to colon carcinoma but no difference in final tumour incidence or frequency (42), the decreased tumour latency by high fat diets might indicate overall differences in tumour incidence at early experimental times. In a recent study, Nicholson et al. (43) showed that a high beef-fat diet did not alter tumour incidence and frequency compared to a low-fat diet. The only difference was that animals fed a high fat diet developed more carcinomas than those fed 5% fat-diet. They suggested that malignant transformation of colorectal adenomas promoted by a high saturated fat diet was associated with an increased colon cell membrane arachidonic acid, the precursor of prostaglandins.

Animals fed 20% lard diet had a significantly higher incidence and frequency of DMH-induced colon tumours (36), increased concentration of total biliary bile acids, faecal acids and faecal neutral sterols than those fed a 5% lard diet. Although the type of fat had no major influence on the incidence of colon tumours in rats fed 20% fat, the animals fed 5% lard diet had a slightly lower incidence of colon tumours than rats fed 5% corn oil. Bansal et al. (44) found that feeding a 30% lard diet accelerated the appearance, frequency and metastases and shortened the survival rate after appearance of the first colon tumour. Rats fed high fat diet had depressed serum immunoglobulin G levels. In addition to the significantly higher incidence and multiplicity of colon tumours, the animals fed 23.5% lard diet during the post initiation phase of AOM-induced carcinogenesis in male F344 rats had a higher excretion of faecal secondary bile acids and increased activity of colonic mucosal ODC than those fed 5% lard diet (45).

### *Trans* Fatty Acids

*Trans* fatty acids are unsaturated fatty acids containing the double-bond *trans*-isomer in place of the natural *cis*-isomer and tend to behave like saturated acids. They occur in the fats of ruminants such as cows or sheep and arise from a hydrogenation process in the animals rumen and during the industrial hardening of vegetable oil. Partially hydrogenated fats, such as margarine and processed vegetable oils constitute the major source of *trans*-fatty acids in the diet.

Nauss et al. (6) demonstrated that although there was a slight increase in the percentage of tumours classified as invasive, the rats fed with a 24% partially hydrogenated fat (Crisco) diet had a significant lower cumulative probability of death compared to those fed 5% fat diet or other high-fat groups. Comparing the effects of dietary monoene type *trans*-fat (partially hydrogenated corn oil) and *cis*-fat (olive oil) on the incidence of DMH-induced colon tumour in rats, Watanabe et al. (46) suggested that *trans* fatty acids were no more cancer promoting than their *cis* counterparts and behaved like the *cis* fatty acids in the modification of chemical-induced colon carcinogenesis, except for steroid excretion. The faecal excretion of neutral but not an acidic steroids was higher in male rats fed the *trans* fatty acids than those fed *cis* fatty acids, but the composition remained almost unchanged. Animals fed a high-fat diet containing various levels of *trans* fatty acids had a lower AOM-induced colon tumour incidence as well as multiplicity of adenocarcinomas compared to those fed a diet containing 23.5% corn oil (47). In contrast to high dietary corn oil, high dietary

*trans* fatty acids had no effect on the concentration of faecal secondary bile acids, however, there was an increase in primary bile acid excretion and the transformation of cholesterol to coprostanol. These findings indicated that dietary *trans* fatty acids influence the composition and activity of intestinal microflora to transform primary to secondary bile acids and cholesterol to coprostanol.

The effect of dietary fat on colorectal cancer is summarised in Table 1. Almost all ω-6 polyunsaturated fatty acids and half of saturated fatty acids promote tumour production while ω-3 polyunsaturated fatty acid protects animals from tumours. The promotional effect is thought to be due to the increased luminal bile acids, colonic mucosal ODC activity and colonic crypt cell proliferation, and reduced host immune function. Whereas the protective effect of fish oil is thought to be due to the inhibition of ODC activity, modulation of lipid metabolism and inhibition of PGE2 synthesis. These results further support the theory that dietary variables or different types of fatty acids rather than total fats in the diet effect the animals' response to colon carcinogens.

**Table 1**
Effect of dietary fat on colorectal cancer

| | Total studies | Promote | No Effect | Protect |
|---|---|---|---|---|
| ω-6 fatty acid | 15 | 14 | 1 | |
| ω-3 fatty acid | 6 | | | 6 |
| Saturated fatty acid | 13 | 6 | 7 | |
| *Trans*-fatty acids | 4 | | 4 | |

## DIETARY FIBRE AND COLON CANCER

Dietary fibres consist of two components *i.e.* soluble fibres, which include pectin, gums, mucilages and some hemicelluloses, and insoluble fibres, which include cellulose, lignin and other hemicelluloses. Soluble and insoluble fibres seem to have disparate effects on colonic physiology and development of DMH or metabolite induced colonic carcinomas in animal models. The former tends to exert its effects on the upper digestive system and is very fermentable in the colon, the latter tends to produce a greater effect on the large bowel increasing faecal bulk and speeding up the rate of colonic transit.

### Insoluble Fibres

**Wheat bran:** Wheat bran is a true food ingredient, containing a relatively high proportion of measurable fibre along with minerals, protein, fat and digestible carbohydrate. DMH and AOM induced carcinogenesis has been reported to be reduced in rodents fed high levels of wheat bran. A significantly lower incidence of DMH induced colorectal tumours has been demonstrated in SD rats fed a diet containing 20% wheat bran (48). Interestingly, lower wheat bran diet (10-15%) with low fat (5%) has consistently been shown to have a protective role in colonic carcinogenesis. In the rodent caecum, wheat bran reduces cell turnover and increases mucosal cell growth caused by diluting bile acids and thereby reducing their damaging effect on colonic epithelium (49). Boffa et al. (50) observed that a 5% wheat bran diet decreased both colonic epithelial cell hyperproliferation and hyperplasia compared to a fibre free diet. They suggested that diets containing moderate amounts of wheat bran may have protective effects on cell proliferation, differentiation, and carcinogenesis; fibre-free diets and diets supplemented with too much fibre would have the potential to promote colon carcinogenesis.

Most studies show that high levels of wheat bran in the diet inhibit colonic carcinogenesis, although not all of studies support this view. Bauer et al. (51) fed 20% wheat bran in a purified, high fat (20%) diet throughout DMH administration and found no effect on tumour incidence or

multiplicity in male SD rat. However, when the fibre was increased to 20 or 30% and the fat reduced to 5% , a reduction of tumour multiplicity was observed. The reason for this is unclear but it may be related to the high fat in the diet. The weak inhibiting effect of wheat bran may be counteracted by the promoting effect of high fat. The same mechanism may explain why no protection was found when 20% wheat bran was added to a non purified diet with 0.5% bile salt, a probable promoter of colon carcinogenesis (52). Cruse et al. (53) reported that 20% wheat bran diet had no effect on overall mortality in female Wistar rats treated with high dose of DMH (total 520 mg/kg). Since other tumours occurred in this model related to the high dose of carcinogen, it is uncertain whether all deaths could be attributed directly to the presence of colon cancer. Recently, Tatsuta (54) found that the addition of 20% wheat bran to the diet had little or no influence on the incidence, number or histology of AOM-induced colonic tumours compared with fibre free diet and inhibited the anticarcinogenic effect of tetragastrin on colonic carcinogenesis. A 20% wheat bran diet has been shown to enhance the incidence and frequency of DMH induced colonic tumours in rats or mice (55,56). This promotion might be associated with stimulation of colonic crypt cell proliferation by wheat bran consumption during DMH administration (55).

**Cellulose:** It has been suggested that DMH and AOM carcinogenesis is reduced in rodents fed high level of cellulose. In a double-blind study, Freeman et al. (57) found that diet containing 4.5% cellulose protected against the development of colonic tumours when compared with a fibre-free diet in male Wistar rats receiving a total of 400 mg/kg DMH. In a further study, the effect of a 4.5% and 9.0% purified cellulose diet fed to higher dose (630 mg/kg) of DMH-treated rats was examined (58). This study indicated that cellulose ingestion significantly reduced the incidence of colon tumours and this effect was dependant on its presence during carcinogen administration but was not dose-dependent. With the higher concentration of dietary cellulose, there was no tumour development in the colon and the few tumours found in the small intestine were significantly smaller and non invasive (59). This reduction of colon carcinogenesis was noted even in the presence of high levels of fat. Heitman et al. (60) showed that the incidence of adenocarcinomas induced by DMH-treatment was decreased with addition of 5 or 10% dietary cellulose during both the initiation and promotion stages of carcinogenesis and during either stage alone. The reduction of DMH- induced tumours in the high-cellulose diet group was associated with distinct changes in the gut bacterial profile and with lower serum cholesterol (61). The protective effect of cellulose might result from decreased activation of bacterial metabolic enzyme beta-glucuronidase rather than physiological effects.

In contrast, one study has reported that cellulose promotes the carcinogenesis in a dose-dependent manner (62). Other studies suggest that cellulose has no effect on DMH induced carcinogenesis (63), although it was found to significantly decrease faecal bile acid concentration and increase daily bile acid excretion (64). A lower luminal pH may be associated with an increased epithelial cell proliferation and a higher tumour yield (63). However, rats fed dietary cellulose with dietary cholesterol demonstrated a lower colonic tumour incidence. This would suggest the protective effect of some fibres in colon carcinogenesis may be dependent on other dietary variables.

**Corn bran:** Of three studies on the effect of dietary corn bran on DMH-induced colon carcinogenesis, only one showed reduction of colonic tumours in rats fed a diet containing 4.5% refined hemicellulose corn bran at 6 months but not at a later time period (65). Moreover, at a 20% level, corn bran-diet enhanced colonic tumour production independent of fat either 20% (66) or 5% (56) in the diet. Although the mechanism of corn bran is not elucidated, some micro component deficiency may be responsible for the promoting effect.

**Phytic acid:** Graf and Eaton (67) hypothesised that dietary phytic acid (inositol hexaphosphate), rather than fibre *per se*, may be the most important determinant of colonic cancer. They suggested that suppression of colonic carcinogenesis and other inflammatory bowel diseases might be due to the inhibition of intracolonic hydroxyl radical (·OH), an iron-mediated hazardous

oxidant (68), via the chelation of reactive iron by phytic acid. Several animal studies have supported this hypothesis. Nelson et al. (69) showed that parenteral supplementation of iron augmented tumour yield and oral iron enhanced tumour incidence in DMH-induced colorectal carcinogenesis (70), while phytic acid was found to reverse the augmenting effect of oral iron on tumour yield and incidence. Shamsuddin et al. (71) showed that 1% phytic acid in drinking water either prior to AOM-treatment or 2 weeks following 6 weekly injection of carcinogen decreased the incidence of colorectal cancer combined with lower mitotic rate and ·OH formation compared to control carcinogen treatment group. The inhibition was noted even when the phytic acid was administered 5 months after the carcinogen (72) and was dose-dependent (73).

In addition to the significantly reduced incidence of colonic tumours, less aberrant crypt foci with four or more crypts (74) and colonic epithelial cell proliferation (75) were found in rats fed phytic acid after injection of AOM. Phytic acid *in vivo* enhanced baseline NK activity and reversed DMH-induced depressed NK activity with an inverse correlation with tumour incidence. *In vitro* enhanced spleen NK cytotoxicity in a dose-dependent manner (76) may be involved in reduced colon tumour formation.

**Soluble Fibres**

**Pectin:** Pectin is a polygalacturonic acid polymer found predominantly in fruits and vegetables. A high level in the diet has been shown to reduce food intake, lower weight gain and significantly inhibit colon tumour incidence (77). Since calorie restriction and subsequent weight loss could decrease tumour incidence (78) the effect of dietary pectin on carcinogenesis has been challenged. A pectin diet fed throughout DMH administration has been found to have no effect whereas if fed during the initiation (51,79) or postpromotion period (65) either it has no effect or enhances colonic carcinogenesis. In contrast to cellulose, greatly increased faecal beta-glucuronidase activity was observed in the animals fed pectin-diet (51, 79). Recently, however, Heitman et al. (80) reported that significant suppressed colon cancer incidence was observed when rats were fed 10% pectin-diet at the promotion stage of carcinogenesis. The role of pectin in experimental colonic carcinogenesis remains controversial.

**Carrageenan:** Carrageenan, an indigestible polysaccharide extracted from red seaweed, enhanced the development of colonic neoplasia in AOM-treated female F344 rats fed at the 15% level with 20% corn oil (81). Increased concentration and daily output of faecal cholesterol, deoxycholic acid and lithocholic acid, as well as the daily output of total bile acids have been noted in Fischer female rats fed a diet containing 15% undegraded carrageenan (82). To investigate if this tumour-promoting effect was due to high fat supplementation, faecal excretion of neutral sterols and bile acid, or colonic mucosal injury, Arakawa et al. (83) fed animals with semipurified diet containing normal levels of fat. They found that carrageenan enhanced colonic carcinogenesis irrespective of beta-glucuronidase activity. They suggested that the promoting effect was mediated by increased excretion of lithocholic acid although there was a decreased concentration of deoxycholic acid and total bile acids in carrageenan-fed rats.

**Psyllium:** Although psyllium hydrophilic mucilloid (metamucil) has been widely used for management of large bowel disorders for many years, its effect on colonic carcinogenesis was only recently investigated. In an early study, 20% metamucil-diet had no protective effect in female Swiss mice and enhanced DMH-induced colonic tumorigenicity in male mice (84). However, 10% psyllium husk-diet containing 20% lard fat reduced the tumorigenicity concomitant with a higher faecal output, percent moisture and aerobic counts, lower beta-glucuronidase and higher 7-a-dehydroxylase activity comparing with control groups (85). Moreover, 5 or 15% of Fybogel, a mucilaginous substance, given at the promotion stage of DMH-induced carcinogenesis inhibited the incidence and yield of colonic tumours.

In summary, although experimental protocols are variable making direct comparisons difficult most insoluble fibres especially wheat bran and cellulose are associated with tumour inhibition while soluble fibres are related to tumour enhancement (Table 2). The tumour inhibitive effect of insoluble fibre is considered to be due to microcomponents in the fibre, such as phytic acid, rather than fibre per se. The potent antioxidant function and enhanced NK activity due to phytic acid are thought to inhibit colorectal carcinogenesis. Wheat bran contains about 4.8% (w/w) phytic acid while no phytic acid is found in corn fibre which enhances tumour production. Furthermore, the reduced tumour production by insoluble fibre can not be explained by the modulation of the physical characteristics of the faeces such as faecal bulk, transit time, short chain fatty acids (SCFA), intestinal microflora, secondary bile acids or pH. However, the tumour enhancement by soluble fibre may be the result of increased SCFA production, microbial metabolic activation of procarcinogens to carcinogens, higher secondary bile acids, a lower pH, or crypt cell hyperproliferation, although the exact mechanism is uncertain.

**Table 2**
Effect of dietary fibre on colorectal cancer

| | Total studies | Promote | No Effect | Protect |
|---|---|---|---|---|
| **Insoluble Fibres** | | | | |
| Wheat bran & Cellulose | 33 | 3 | 9 | 21 |
| Corn bran | 3 | 2 | 1 | |
| Phytic acid | 6 | | | 6 |
| **Soluble Fibres** | | | | |
| Pectin | 7 | 3 | 2 | 2 |
| Psyllium | 3 | 1 | | 2 |
| Carrageenan | 2 | 2 | | |

## CONCLUSIONS

The effect of dietary fat and fibre on DMH- and its metabolites-induced colonic carcinogenesis has been extensively investigated. An enhancement or promotion of colonic tumours is generally associated with total dietary fat intake. Diet containing high level of ω-6 polyunsaturated fatty acid is more effective than that of saturated and monounsaturated fat in promoting colonic carcinogenesis, whereas ω-3 polyunsaturated fatty acid has no promoting effect or may have a protective role. Different sources of dietary fibres produce markedly different effects on colon carcinogenesis. Some fibres seem to inhibit tumour formation, while others clearly enhance tumour development. These findings suggest that the quality as well as quantity of total dietary supplementation have an important role to play in modulating experimental colonic carcinogenesis. Though the mechanisms in which dietary fat and fibre exert their effect on colorectal tumour formation and development need further explanation, it is plausible to encourage people to eat less fat and more vegetable and fruit, hence more fibre.

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