Dietary effects of menhaden oil on the growth and membrane lipid composition of rat mammary tumors.

Jurkowski JJ, Cave WT Jr.

The objective of this study was to evaluate the effect of quantitative differences in dietary menhaden oil, an n-3 polyunsaturated marine oil, on mammary tumor development and to compare these results with those produced by corn oil, an n-6 polyunsaturated vegetable oil. Inbred female BUF rats were treated with the carcinogen N-methyl-N-nitrosourea (CAS: 684-93-5) and maintained on diets containing graded levels of each of the respective oils. Our results indicated that diets containing 20% menhaden oil produced a reduction in tumor incidence and a prolongation of the tumor latent period. This finding contrasted sharply with the enhanced tumor development and shortened latent period observed in the animals fed the equivalent dietary level of corn oil. Fatty acid analyses performed on the lipids extracted from the tumor and hepatic microsomes of the animals on the menhaden oil diets demonstrated that the proportion of eicosapentaenoic acid (No. of C-atoms:No. of double bonds = 20:5) present in these microsomal lipids was related inversely to mammary tumor development.

Dietary intervention during the postdosing phase of L-azaserine-induced preneoplastic lesions.

O'Connor TP, Roebuck BD, Campbell TC.

The effects of intervention by diets with high or low levels of dietary fat on the development of preneoplastic pancreatic lesions were examined. Wistar rats were treated ip at 14 days of age with a 30-mg/kg dose of L-azaserine [CAS: 115-02-6; diazoacetate serine (ester)] and weaned onto the test diets. Animals fed 5% corn oil had fewer preneoplastic lesions compared to animals fed 20% corn oil throughout the 4-month posttreatment period. The strong response observed in rats fed 20% corn oil could be markedly reduced by intervention with a 5% corn oil diet halfway through the posttreatment period. Similarly, the low response in animals fed 5% corn oil could be markedly elevated by intervention with a high-fat diet. These results provide evidence for the hypothesis that tumor development may be modified by dietary means.

Dietary polyunsaturated fat in relation to mammary carcinogenesis in rats.

Braden LM, Carroll KK.

High fat diets promote the development of mammary tumors induced in rats by 7,12-dimethylbenz(a)anthracene (DMBA), and polyunsaturated fats are more effective than saturated fats. This difference is related to the linoleic acid content of polyunsaturated vegetable oils, but the amount of linoleate required for maximum tumor promotion appears to be higher than indicated by earlier experiments. Comparison of the effects of a polyunsaturated vegetable oil (corn oil) containing linoleate with a fish oil (menhaden oil) containing polyunsaturated fatty acids derived from linolenic acid showed that higher dietary levels of corn oil increased the yield of DMBA-induced mammary tumors, while corresponding levels of menhaden oil had an inhibitory effect. This is further evidence that promotion of mammary tumorigenesis by polyunsaturated vegetable oils may be mediated by prostaglandins or other biologically active eicosanoids derived from n-6 fatty acids.


Effect of dietary menhaden oil on tumor cell loss and the accumulation of mass of a transplantable mammary adenocarcinoma in BALB/c mice.

Gabor H, Abraham S.

A reduction in the size of transplantable mammary adenocarcinoma IX was achieved when female BALB/c mice were fed isocaloric 10% fat diets containing either hydrogenated cottonseed oil (HCTO) or menhaden oil (MO) as opposed to those mice fed corn oil (CO). Indeed, CO increased the size of the neoplasms when fed alone at 5 or 1% of the diet, although such diets contained less fat calories than did the 10% fat diets containing the other two oils. At the 10% level of dietary fat, enhanced accumulation of tumor mass was observed even when 7.5, 5.0, and 2.5% CO was administered in combination with either HCTO or MO. Although this effect of CO could not be inhibited when nine times as much HCTO was added to the diet, such growth enhancement was abolished when the diet contained nine times as much MO. Hence these experiments emphasized the importance of the type rather than the amount of dietary fat. Whereas MO contained polyunsaturated fatty acids (PUFA's) [approximately 1% as linoleic acid, approximately 16% as 5,8,11,14,17-eicosapentaenoic acid (EPA), approximately 11% as 4,7,10,13,16,19-docosahexaenoic acid (DHA)], HCTO contained none and CO had about 60% of its constituent fatty acids in the form of linoleic acid. The rate of tumor cell loss, determined by the [125I]5-iodo-2'-deoxyuridine method, in the 10% MO-fed or the 10% HCTO-fed mice (54 or 45%, respectively) was more than twice that observed for tumors from the 10% CO-fed mice (22%). These observations were discussed in terms of the influence of the dietary PUFA linoleic acid [C 18:2 (No. of carbons:No. of double bonds), n-6], the PUFA EPA (C 20:5, n-3), and the PUFA DHA (C 22:6, n-3) on the size of mammary tumors and on the involvement of prostaglandins in this process.
Effect of dietary fish oil on azoxymethane-induced colon carcinogenesis in male F344 rats.

Reddy BS, Maruyama H.

The effect of dietary intake of different levels of Menhaden fish oil on azoxymethane-induced carcinogenesis was examined in male F344 rats fed the semipurified diets. Starting at 5 weeks of age, groups of animals were fed the 5% corn oil (low corn oil) diet. At 7 weeks of age, all animals except the vehicle-treated controls were given s.c. injections of azoxymethane (15 mg/kg body weight/week for 2 weeks). After 4 days, groups of animals were fed the diets containing 4% Menhaden oil + 1% corn oil (low fish oil), 22.5% Menhaden oil + 1% corn oil (high fish oil), 5% corn oil, and 23.5% corn oil (high corn oil). Thirty-four weeks after azoxymethane injections, all animals were necropsied. High fish oil diet had no tumor promoting effect in the large intestine when compared to the high corn oil diet. There was no difference in large intestinal tumor incidence among the other dietary groups. The results of this study indicate that fish oils rich in highly polyunsaturated n-3 fatty acids do not enhance large bowel carcinogenesis and that the fatty acid composition of the dietary fat is one of the determining factors in large bowel carcinogenesis.

A comparison of dietary fish oil and corn oil in experimental colorectal carcinogenesis.


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Rats fed either fish oil (n = 16) or corn oil (n = 16) in calorically and nutritionally balanced diets were injected with 1,2-dimethylhydrazine, which is a colorectal specific carcinogen; differential colorectal tumor induction was then measured. In addition, plasma peroxide concentrations were measured in rats in each dietary group as well as in a group receiving a low-fat diet, either with or without prior carcinogen treatment (n = 3 for each of the 6 groups). Tumor incidence did not differ between groups fed corn oil and fish oil. Tumor yield in the left colon was significantly lower in rats fed fish oil (p = 0.0499). Total colorectal tumors induced were also fewer in the rats fed fish oil (p = 0.065). Plasma peroxide concentrations were difficult to interpret because of the wide variation within groups. The data on tumor yield in the left colon support the hypothesis that a diet rich in n-3 fatty acids, which are found in fish oil, may be less supportive of colorectal tumor development than a diet rich in n-6 fatty acids, which is found in corn oil. However, the mechanism by which fish oil decreases tumor induction is still unknown.
Effect of dietary omega-3 and omega-6 fatty acids on development of azaserine-induced preneoplastic lesions in rat pancreas.

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We examined the effect of varying the ratio of dietary omega-3 (omega 3) to omega-6 (omega 6) on the development of pancreatic preneoplastic lesions in male Wistar rats given azaserine at 14 days of age. As the ratio of dietary omega 3 to omega 6 fatty acids increased in a diet totaling 20% by weight of fat, the development of preneoplastic atypical acinar cell nodules (AACNs) at 4 months after dosing with azaserine decreased significantly. In addition, serum levels of prostaglandin thromboxane B2, prostaglandin E2, and 6-keto-prostaglandin F1 alpha decreased significantly. The fatty acid composition of the rbc membrane was also significantly influenced by the ratio of dietary omega 3 to omega 6 fatty acids. In a second experiment, we examined the effect of dietary intervention with a different type of fat (corn oil or menhaden oil) 2 months into the 4-month postdosing period on AACN development at the end of the post-dosing period. Intervention of the omega 6 fatty acid-rich diet with the omega 3 fatty acid-rich diet significantly decreased focal development. The opposite was true when intervention involved substituting the omega 3 fatty acid-rich diet with the omega 6 fatty acid-rich diet.

Enhancing effect of high fat diet on 4-nitroquinoline 1-oxide-induced pulmonary tumorigenesis in ICR male mice.

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The effects of dietary high fat on 4-nitroquinoline 1-oxide (4NQO)-induced lung tumorigenesis were investigated in male ICR mice. Two groups of mice were initially given a single subcutaneous injection of 4NQO at a dose of 15 mg/kg and, thereafter, fed either 20% corn oil-supplemented diet or a standard basal diet. Two further groups were maintained on the high fat diet or standard diet without administration of 4NQO. Mice were killed at weeks 15, 18 and 25 and the incidence of lung tumors at each time point was found to be significantly increased in the 4NQO/high fat diet group as compared to the 4NQO/standard diet group in terms of both incidence of tumor-bearing mice and the number of lesions per mouse. The results thus indicate that dietary high fat can enhance 4NQO-induced lung tumorigenesis in mice.
Effects of dietary perilla oil, soybean oil and safflower oil on 7,12-dimethylbenz[a]anthracene (DMBA) and 1,2-dimethyl-hydrazine (DMH)-induced mammary gland and colon carcinogenesis in female SD rats.

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The effects of diet supplemented with perilla oil, which contains a large amount of n-3 alpha-linolenic acid, and n-6 linoleic acid rich soybean and safflower oil supplemented diets on 7,12-dimethylbenz[a]anthracene (DMBA)- and 1,2-dimethyl-hydrazine (DMH)-induced mammary gland and colon carcinogenesis were investigated in female SD rats. Groups of 23 or 24, 5 week old animals were first given three s.c. injections of 40 mg/kg body wt DMH followed by a single intragastric administration of 50 mg/kg body wt DMBA within 2 weeks of the commencement. Starting 1 week after the DMBA treatment, they were administered pellet diet containing 10% perilla oil, soybean oil or safflower oil for the succeeding 33 weeks. Histological examination revealed that the resultant numbers of mammary tumors per rat were significantly lower in rats given perilla oil diet (4.4 +/- 2.5) than in the soybean oil diet group (6.5 +/- 3.9). Furthermore, colon tumor incidence was significantly lower in animals receiving the perilla oil supplement (18.2%) than in those given safflower oil diet (47.4%), and the numbers of colon tumors per rat tended to be lowest in rats administered perilla oil. Also the incidence of nephroblastomas in rats receiving perilla oil diet (0%) was significantly lower than that for the soybean oil diet group (23.8%). The results thus indicate that the alpha-linolenic acid (n-3)-rich perilla oil diet inhibits development of mammary gland, colon and kidney tumors as compared to linoleic acid (n-6)-rich safflower or soybean oil diet.

Inhibitory effect of dietary perilla oil rich in the n-3 polyunsaturated fatty acid alpha-linolenic acid on colon carcinogenesis in rats.


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The inhibitory effect of dietary perilla oil rich in the n-3 polyunsaturated fatty acid alpha-linolenic acid against colon carcinogenesis was investigated in rats. Four groups of 26 F344 rats each received an intrarectal dose of 2 mg of N-methyl-N-nitrosourea 3 times a week for 2 weeks, and received a diet containing 12% perilla oil, 6% or 12% safflower oil (rich in the n-6 polyunsaturated fatty acid linoleic acid), or 12% palm oil (rich in saturated and monounsaturated fatty
acids). At week 35, the incidence of colon cancer was significantly lower in perilla oil-fed rats than in other dietary groups; 19% vs. 46%, 56% and 58%. When examined at week 10, the concentration of fecal bile acids, known to be tumor promoters, was not significantly different among the dietary groups, and the intrarectal deoxycholic acid-induced colonic mucosal ornithine decarboxylase activity, a marker of tumor promotion, was significantly lower in perilla oil-fed group than in other groups. The serum and colonic mucosal fatty acid compositions and the blood plasma prostaglandin E2 level directly reflected the fatty acid composition of each dietary fat. The results suggest that the anti-tumor-promoting effect of dietary perilla oil was a result of a decreased sensitivity of colonic mucosa to tumor promoters arising from the altered fatty acid composition in membrane phospholipid of colonic epithelial cells, and was not a consequence of a decrease of promoters such as bile acids.


**Flaxseed supplementation and early markers of colon carcinogenesis.**

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Since flaxseed ingestion produces potentially anticarcinogenic lignans in the colon, this study determined whether flaxseed decreases the risk for colon carcinogenesis. Following a single injection of azoxymethane (15 mg/kg body wt.), five groups of male Sprague-Dawley rats were fed a high-fat (20% corn oil) basal diet with or without supplementation with 5% or 10% flaxseed meal (FM) or flaxseed flour (FF) for four weeks. Upon sacrifice, colons were examined for aberrant morphology and cell proliferation. In the descending colon of supplemented groups, the total number of aberrant crypts and foci were significantly reduced by 41-53% and 48-57%, respectively. The labeling index (LI) was also 10-22% lower in these groups, except for the 5% FM group. While these effects are not linearly related to the level of flaxseed fed, it suggests that flaxseed feeding may reduce the risk for colon carcinogenesis.


**Adipose tissue omega-3 and omega-6 fatty acid content and breast cancer in the EURAMIC study. European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer.**

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The fatty acid content of adipose tissue in postmenopausal breast cancer cases and
controls from five European countries in the European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Cancer (EURAMIC) breast cancer study (1991-1992) was used to explore the hypothesis that fatty acids of the omega-3 family inhibit breast cancer and that the degree of inhibition depends on background levels of omega-6 polyunsaturates. Considered in isolation, the level of omega-3 or omega-6 fat in adipose tissue displayed little consistent association with breast cancer across study centers. The ratio of long-chain omega-3 fatty acids to total omega-6 fat showed an inverse association with breast cancer in four of five centers. In Malaga, Spain, the odds ratio for the highest tertile relative to the lowest reached 0.32 (95% confidence interval 0.13-0.82). In this center, total omega-6 fatty acid was strongly associated with breast cancer. With all centers pooled, the odds ratio for long-chain omega-3 to total omega-6 reached 0.80 for the second tertile and 0.65 for the third tertile, a downward trend bordering on statistical significance (p for trend = 0.055). While not definitive, these results provide evidence for the hypothesis that the balance between omega-3 and omega-6 fat may play a role in breast cancer.