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Effect of Dietary Fish Oil on Azoxymethane-induced Colon Carcinogenesis in Male F344 Rats[1]

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ABSTRACT

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.

INTRODUCTION

Epidemiological studies have shown that diets particularly high in total fat and animal fat or low in certain fibers are generally associated with an increased risk for colon cancer development (1–6), although a recent prospective study showed no increased effect of dietary saturated fat or total fat in colon cancer (7). Discrepancies in epidemiological studies might have stemmed from methodological problems of dietary assessment, because several of these studies not only rarely distinguished between the types of saturated and polyunsaturated fats consumed but did not take into consideration other confounding factors such as dietary fiber. Several animal model studies demonstrated that high fat diets containing corn oil, safflower oil, lard, or beef tallow enhanced the chemically induced colon tumors in rats, whereas the diets containing high levels of coconut oil, olive oil, or *trans*-fat had no colon tumor-promoting effect (8–14). However, another study suggests no enhancing effect of dietary beef tallow or corn oil on colon tumors (15). These studies suggest that the fatty acid composition of the fat is an important determining factor in colon tumorigenesis.

Interest in the marine oils emerged from the observation that cancer incidence rates are generally low in Alaskan and Greenland Eskimos compared to American whites and other western populations, despite the fact that these defined populations eat high-fat diets (16–19). Although fish oils are rarely found in western diets, Eskimo diets contain large amounts of oils derived from fish and seals (20–22). The high amount of highly polyunsaturated (n-3 series) fatty acids such as eicosapentaenoic acid (C20:5, n-3) and docosahexaenoic acid (C22:6, n-3) present in fish oils make them unique dietary fats (23, 24). Recent studies in animal models demonstrated that high levels of dietary Menhaden fish oil had no promoting effect on 7,12-dimethylbenz(*a*)anthracene-induced (25) and methylnitrosourea-induced (26) mammary carcinogenesis when compared to high dietary corn oil in rats. Dietary intake of 20% Menhaden oil when compared to 20% corn oil produced a significant inhibition in both size and number of preneoplastic lesions in rat pancreas (27). Karmali *et al.* (28) reported that daily treatment of 0.2 ml Max EPA, a commercially available fish oil, inhibited growth of transplantable mammary tumors in rats. The present study was designed to investigate the modifying effect of dietary fish oil on AOM[3]-induced large intestinal carcinogenesis in rats.

MATERIALS AND METHODS

Animals, Diets, and Carcinogen. A total of 124 weanling male F344 rats were purchased from Charles River Breeding Laboratories (Wilmington, MA). All semipurified dietary ingredients were from Dyets, Inc. (Bethlehem, PA), and AOM (CAS:25843-45-2) was from Ash-Stevens, Inc. (Detroit, MI). Menhaden fish oil was donated by Zapata Haynie Corporation (Reedville, VA).

Male F334 rats received at weaning were quarantined for 10 days and then randomly assigned into 4 dietary groups of 36 animals each. Each dietary group was divided into AOM-treated (24 animals) and vehicle-treated (12 animals) subgroups and housed 3 to a plastic cage with filter tops in the animal holding room under controlled environmental conditions of a 12-h light-dark cycle, 50% humidity, and 21°C. All animals were fed *ad libitum* and had free access to water. The food cups were replenished every day.

The composition of experimental semipurified diets is shown in Table 1 and is based on revised AIN-76 diet (29, 30). The composition of high- and low-fat diets was adjusted so that the animals in all dietary groups would consume the same amount of calories, protein, vitamins, minerals, and fiber (14, 31). All diets were prepared in our laboratory 3 times weekly and stored in a cold room at 4°C. Corn oil (1%) was added to low and high Menhaden fish oil diets to provide linoleic acid and to alleviate essential fatty acid deficiency. Freshly prepared diets and those stored for 2 days in a cold room were analyzed for peroxides using thiobarbituric acid method (32). There were no detectable levels of peroxides in the diets.

The fatty acid composition of Menhaden fish oil was analyzed and provided by Zapata Haynie Corporation. It contained about 15% palmitic acid (C16:0), 12% palmitoleic acid (C16:1, n-6), 10% oleic acid (C18:1, n-6), 16% eicosapentaenoic acid (C20:5, n-3), 11% docosahexaenoic acid (C22:6, n-3), and 1.8% linoleic acid (C18:2, n-3). Corn oil contains about 10% palmitic acid, 31% oleic acid, and 56% linoleic acid (33). Menhaden fish oil and corn oil contained about 25 and 150 ppm of α-tocopherol, respectively.

Experimental Procedure. Starting at 5 weeks of age, all animals were fed the experimental diet containing 5% corn oil and continued on this diet until 4 days after carcinogen or vehicle treatment. At 7 weeks of age, animals intended for carcinogen treatment in each subgroup were given s.c. injections of AOM (15 mg/kg body wt/wk) once weekly for 2 weeks, whereas the animals intended for vehicle treatment were given

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[3] The abbreviation used is: AOM, azoxymethane.

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Table 1 *Composition of experimental diets*

Diet ingredients	Menhaden oil diets		Corn oil diets	
	Low-fat[a]	High-fat[b]	Low-fat[a]	High-fat[b]
Casein, vitamin-free	20.0	23.50	20	23.50
DL-Methionine	0.3	0.35	0.3	0.35
Corn starch	52.0	32.90	52.0	32.90
Dextrose	13.0	8.30	13.0	8.30
Alphacel	5.0	5.90	5.0	5.90
Corn oil	1.0	1.00	5.0	23.52
Menhaden oil	4.0	22.52	0	0
Mineral mix, AIN	3.5	4.11	3.5	4.11
Vitamin mix, AIN revised	1.0	1.18	1.0	1.18
Choline bitartrate	0.2	0.24	0.2	0.24

[a] This diet was prepared on the basis of the American Institute of Nutrition (AIN) Standard Reference Diet (29, 30) with modification of varying sources of carbohydrate.

[b] The composition of high-fat diets was adjusted so that the intake of protein, minerals, vitamins, fiber, and calories in animals in the different dietary groups was the same (14).

an equal volume of normal saline. Prior to injection, AOM was dissolved in normal saline. Four days after AOM or vehicle treatment, groups of animals started with 5% corn oil diet were transferred to diets containing 4% Menhaden fish oil + 1% corn oil (designated as low Menhaden oil diet), 22.5% Menhaden fish oil + 1% corn oil (high Menhaden oil diet), or 23.5% corn oil (high corn oil diet). An additional group consuming the 5% corn oil diet (low corn oil diet) was continued on the same diet. All animals were fed the experimental diets until termination of the experiment. The experiment was terminated 34 weeks post-AOM treatment. Body weights were measured weekly until the animals attained 16 weeks of age and then every 4 weeks until the termination of the experiment. Food consumption was measured for a period of 1 week at the end of 12 and 22 weeks on experimental diets.

Four animals treated with AOM from each dietary group were endoscoped 20 and 30 weeks after the last AOM injection, since endoscopic examination of the colon reveals the presence and size of tumors in the lower part of the colon without sacrificing the animals. Not only were the tumors that were present in animals endoscopically examined at 20 weeks after the last AOM injection also observed at 30 weeks, but also the size of these tumors was increased at 30 weeks. The experiment was terminated 34 weeks after the last AOM injection. Both AOM- and vehicle-treated animals were sacrificed by CO_2 euthanasia as scheduled. At autopsy, all organs, including intestines, were examined grossly under the dissection microscope for tumors. Tissues were fixed in 10% buffered formalin and embedded in paraffin. Paraffin-embedded tissue sections were then stained with hematoxylin and eosin and examined histologically for tumor types. Each tumor was classified according to histological criteria (34).

Statistical Analysis. The tumor data were analyzed by the χ^2 method, Fisher's exact test, and Student's *t*-test.

RESULTS

Body Weights and Food Consumption. Animals fed the high Menhaden oil diet and treated with AOM or vehicle weighed less than those fed the other diets (Table 2). The decrease in body weight of animals fed the high Menhaden oil diet was observed starting at 8 weeks on this diet. On the other hand, body weights of animals fed the corn oil diets and low Menhaden oil diet were comparable throughout the experimental period. Food consumption measured at the end of 12 and 22 weeks on experimental diets indicated that the animals fed the low corn oil or low Menhaden oil diets consumed about 12–13% more food than those fed the high corn oil or high Menhaden oil diets. There was no difference in food intake between low corn oil and low Menhaden oil groups or among high corn oil and high Menhaden oil groups. Except for the number of calories from fat in the diet, the intakes of protein, vitamins, minerals, non-nutritive fiber, and total calories were similar in all dietary groups.

Tumor Incidences. Table 3 summarizes the AOM-induced large intestinal tumor incidence and multiplicity in animals fed various diets. There was no evidence of tumor incidence in vehicle-treated animals. Large intestinal tumor incidence (number of animals with tumors) and large intestinal tumor multiplicity (number of adenomas and adenocarcinomas/animal) were significantly lower in animals fed low and high Menhaden oil diets and the low corn oil diet than in animals fed the high corn oil diet. The incidence of large intestinal tumors did not differ significantly among the groups fed low and high Menhaden oil diets and the low corn oil diet. There was no statistically significant difference in the multiplicity of adenomas and adenocarcinomas between the groups fed the low and high Menhaden oil diets.

Table 4 shows the AOM-induced tumor incidence in small intestine and ear duct. Tumors of the small intestine were adenomas and adenocarcinomas, whereas tumors of the ear duct were squamous cell carcinomas. Small intestinal tumors were all localized in the duodenum. Low and high Menhaden oil diets or low and high corn oil diets had no significant effect on small intestinal and ear duct tumor incidences.

DISCUSSION

The results of the present study not only confirm our previous study in female rats (14) that a diet containing high corn oil significantly increased the AOM-induced large intestinal tumor incidence and multiplicity compared to a low corn oil diet but extends our observation that a high Menhaden oil diet had no tumor enhancing effect in the large intestine compared to a high corn oil diet. We are not aware of any previous study of a potential large intestinal tumor inhibitory effect by a fish oil diet. Recent studies demonstrated that diets containing 20% Menhaden oil induced fewer 7,12-dimethylbenz(*a*)anthracene- or methylnitrosourea-induced mammary tumors, as well as produced a significant reduction of the development of both the size and number of L-azaserine-induced preneoplastic lesions in the pancreas when compared to a diet containing 20% corn oil (25, 26, 28).

The lack of large bowel tumor promoting effect of high dietary Menhaden oil observed in this study and that of high dietary olive oil, coconut oil, and *trans*-fat observed in our previous study (11, 14), in contrast to that of high dietary corn oil, safflower oil, beef fat, and lard (3, 8) suggests that the fatty acid composition of a dietary fat is one of the determining factors in large bowel carcinogenesis. It has been demonstrated that the excretory pattern of fecal secondary bile acids, namely deoxycholic acid and lithocholic acid, which have been shown to act as large bowel tumor promoters, positively correlated with large bowel tumor incidence in animal models fed various types and amounts of dietary fat (35). Although the present study was not designed to address this aspect of the influence of dietary fish oil on colonic secondary bile acids, it is likely that high dietary fish oil may have an inhibitory effect on the colonic concentration of secondary bile acids. In addition, we should not rule out the possibility that the effect of different types of fat on large bowel carcinogenesis might be mediated by the active products of essential fatty acids such as prosta-

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Table 2 *Body weights of male F344 rats treated with AOM or vehicle and fed the experimental diets*

Diet group	No. of rats at start of experiment	Body wt. (g) on experimental diets at week: Initial wt. (week 0)	4	8	18	26	34	37 (at termination)
AOM-treated								
Low Menhaden oil	24	39 ± 5[a]	185 ± 11	262 ± 12	354 ± 16	393 ± 21	428 ± 26	438 ± 26
High Menhaden oil	24	40 ± 4	180 ± 11	246 ± 16	330 ± 19	370 ± 24	370 ± 26	370 ± 18
Low corn oil	24	41 ± 4	179 ± 9	258 ± 7	369 ± 22	397 ± 24	423 ± 27	426 ± 34
High corn oil	24	40 ± 4	184 ± 11	273 ± 18	360 ± 20	405 ± 27	432 ± 30	437 ± 33
Vehicle-treated								
Low Menhaden oil	12	38 ± 3	190 ± 7	280 ± 10	369 ± 18	400 ± 29	447 ± 32	456 ± 36
High Menhaden oil	12	40 ± 3	187 ± 15	268 ± 17	345 ± 13	385 ± 21	388 ± 28	390 ± 20
Low corn oil	12	41 ± 4	195 ± 11	286 ± 11	384 ± 9	430 ± 14	468 ± 15	470 ± 17
High corn oil	12	41 ± 5	201 ± 10	281 ± 18	380 ± 26	423 ± 30	457 ± 31	464 ± 33

[a] Mean ± SD.

Table 3 *AOM-induced large bowel tumors in male F344 rats fed the diets containing low and high amounts of Menhaden fish oil or corn oil*

Diet group	Total no. of animals	Tumor incidence (animals with large bowel tumors) Total[a]	Adenoma	Adenocarcinoma	Tumor multiplicity (large bowel tumors/animal) Total	Adenoma	Adenocarcinoma
AOM-treated							
Low Menhaden oil	24	12(50)[b,c]	10(42)[c]	4(17)[c]	0.63 ± 0.71[c,d,e]	0.46 ± 0.59[c,e]	0.17 ± 0.38[c]
High Menhaden oil	24	8(33)[c]	5(21)[c]	4(17)[c]	0.38 ± 0.57[c]	0.21 ± 0.41[c]	0.17 ± 0.38[c]
Low corn oil	24	13(54)[c]	11(46)[c]	6(25)[c]	0.92 ± 0.50[e]	0.54 ± 0.42[e]	0.38 ± 0.39[c]
High corn oil	24	22(92)[e]	19(79)[e]	15(63)[e]	1.96 ± 0.48[f]	0.96 ± 0.49[f]	1.00 ± 0.44[e]
Vehicle-treated	48	0	0	0	0	0	

[a] Total represents animals with both adenomas and/or adenocarcinomas.
[b] Numbers in parentheses, percentage
[c,e,f] Means in the same column that do not share a common superscript are significantly different at $P < 0.05$ (χ^2 test and Student's *t*-test).
[d] Mean ± SD.

Table 4 *AOM-induced tumor incidences in male F344 rats fed the diets containing low and high amounts of Menhaden fish oil or corn oil diets*

Diet group	Small intestinal tumors: % of animals with tumors	Tumors/animal	% of animals with ear duct tumors
Low Menhaden oil	25[a]	0.29 ± 0.55[a,b]	8[a]
High Menhaden oil	17[a]	0.17 ± 0.38[a]	0[a]
Low corn oil	25[a]	0.33 ± 0.54[a]	8[a]
High corn oil	25[a]	0.38 ± 0.58[a]	12[a]

[a] Means in the same column that do not share a common superscript are significantly different at $P < 0.05$ (χ^2 test and Student's *t*-test).
[b] Mean ± SD.

glandins, since recent studies demonstrated an inhibitory effect of certain prostaglandin synthesis inhibitors (indomethacin) on chemically induced large bowel carcinogenesis in rats (36, 37). In the present study, low and high Menhaden oil diets and low and high corn oil diets contained, respectively, about 0.6, 1.0, 2.8, and 13.2% linoleic acid, a precursor for prostaglandin synthesis. Eicosapentaenoic acid present in Menhaden oil has been shown to be a competitive inhibitor of cyclooxygenase, which is the first enzyme in the synthesis of prostaglandins (38). Docosahexaenoic acid present in Menhaden fish oil exerts an inhibitory effect on the metabolism of arachidonic acid and thus inhibits synthesis of dienoic prostaglandins (39). It is possible that the lack of a large bowel tumor promoting effect by Menhaden oil might be due to its inhibitory effect on prostaglandin synthesis as proposed for mammary carcinogenesis (23).

The question also arises as to whether the lack of a large bowel tumor promoting effect of high Menhaden oil diet might be related to the weight loss. Although the food intake was not measured throughout the study, calorie intake measured during 12 and 22 weeks on the experimental diets was similar in all dietary groups. Although a difference in body weights as much as 30% in animals fed various experimental diets did not correlate with large bowel tumor incidence in our previous study (40), it is possible that diminished weight gain in animals fed the high Menhaden oil diet may have contributed to reduced tumor incidence. Additional studies are needed for a better understanding of the overall effect of marine oils in large bowel carcinogenesis.

In conclusion, the present study demonstrates that high dietary Menhaden oil (*a*) induces fewer large bowel tumors than did the diet containing high corn oil and (*2*) does not promote large bowel carcinogenesis to any greater extent than does a diet containing either low Menhaden oil or low corn oil.

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