NUTRITION AND CANCER, *52*(2), 121–129

Nutritional Intervention With Omega-3 Fatty Acids in a Case of Malignant Fibrous Histiocytoma of the Lungs

Ronald S. Pardini, David Wilson, Steven Schiff, Stephen A. Bajo, and Randall Pierce

Abstract: *We present a case of a 78-yr-old man with malignant fibrous histiocytoma with multiple lesions in both lungs. Following diagnosis, he declined conventional chemotherapy and elected nutritional intervention by increasing intake of omega-3 fatty acids and lowering intake of omega-6 fatty acids. We estimated that he consumed 15 g of the long-chain omega-3 fatty acids eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) per day, and the ratio of linoleic acid/long-chain omega-3 fatty acids in his diet was 0.81. Serial computed tomography scans and pulmonary x-rays revealed remarkably a slow and steady decrease in the size and number of bilateral nodules. He has no apparent side effects from consuming large quantities of fish and algae oils rich in DHA and EPA and he remains asymptomatic.*

Introduction

Malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma of the elderly. MFH arising from the lungs is rare, although the lungs are the primary sites of metastasis (1–3). Lung MFH has a poor prognosis, and early diagnosis with timely surgical resection is the most common treatment resulting in long-term survival (3).We report on a case of a man (DH) in his 8th decade who was diagnosed with lung MFH, who altered his diet to consume high quantities of omega-3 fatty acids and limit his intake of common vegetable oils. This nutritional modification significantly altered the ratio of omega-6 to omega-3 fatty acids in his diet. The rationale for this nutritional intervention stems from epidemiological and experimental findings that suggest a relationship between the level of omega-3 fatty acids in the diet and tumorigenesis. Eskimos from Alaska and Greenland consume higher amounts of omega-3 fat and exhibit a lower incidence of colon, breast, and prostate cancer than other North Americans (4,5). Reports of the decreased risk of colon and breast cancer with increasing consumption of fish and fish oil (6,7) suggest that omega-3 fatty acids play a role in decreasing cancer risk. In a case-controlled study in women, the consumption of fish oil protected against the development of colorectal cancer (8), and epidemiological studies support the hypothesis that consumption of a diet rich in omega-3 fatty acids reduces the risk of breast and prostate cancer (9–11). Similarly, a population-based prospective study with 5,885 residents concluded that frequent consumption of fresh fish reduced the risk of lung cancer (12).

In laboratory animal models, nutritional intervention with high levels of dietary fat rich in omega-3 fatty acids resulted in decreased growth of a variety of mammary, prostate, and colon tumors (13–26). In a series of studies employing human mammary, colon, prostate, and ovarian carcinomas grown in athymic "nude" mice, consumption of diets rich in fish oil containing the long-chain polyunsaturated omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) resulted in decreased rates of tumor growth from 50 to 75% (16,18,27). Feeding diets rich in golden algae oil containing only one omega-3 fatty acid, DHA, suppressed human prostate and colon tumor growth in athymic mice by 75 and 90%, respectively (18,27), and was preferentially inhibitory to mammary carcinoma (19,20), suggesting that DHA was the primary tumor-suppressing long-chain omega-3 fatty acid. This conclusion was verified in culture with human colon carcinoma WiDr and COLO 205 and prostate carcinoma LNCaP and PC-3, which were all preferentially inhibited by DHA and not EPA (27). Human lung mucoepidermoid carcinoma (28) and A427 lung adenocarcinoma (29) growth in athymic mice were depressed by feeding diets rich in EPA and DHA, and various sarcoma tumor lines were also inhibited in vitro (30,31) and in vivo (31–33) by long-chain omega-3 polyunsaturated fatty acids (PUFAs). The broad spectrum of experimental tumors inhibited by long-chain omega-3 PUFAs influenced DH to alter his diet and supplement it with long-chain omega-3 fatty acids. Because of the findings in animal studies that DHA is the most potent tumor-suppressing fatty acid (18–20,27), DH fashioned his supplemental schedule to include high levels of DHA intake.

R. S. Pardini is affiliated with the Department of Biochemistry, College of Agriculture, Biotechnology and Natural Resources, University of Nevada, Reno NV 89557. D. Wilson is affiliated with the Department of Nutrition, College of Agriculture, Biotechnology and Natural Resources, University of Nevada, Reno NV 89557. S. Schiff, S. A. Bajo, and R. Pierce are affiliated with the School of Medicine, University of Nevada, Reno NV 89557.

Results: Case History

DH is a 78-yr-old man who presented in January 2000 with complaints of cough for 6 mo. He quit tobacco use in 1965 after smoking a half of a pack of cigarettes a day for 23 yr. A chest x-ray demonstrated bilateral pulmonary nodes. An abdominal computed tomography (CT) scan revealed only pulmonary nodules with no disease below the diaphragm. No evidence of another primary site was found. He had no previous history of neoplastic disease with the exception of prior localized skin cancer. On July 24, 2000, he underwent fine-needle aspiration and biopsy of the right lung nodule that revealed histological and immunochemical features consistent with a spindle cell neoplasm, which was diagnosed on September 31, 2000, as MFH. Fine-needle aspirate smear showed aggregates of cytologically malignant cells with spindloid and epitheloid appearance. Some cells contained small amounts of brown pigment that is more suggestive of hemosiderin than melanin. Sections of the tissue fragments showed histological features that confirmed the cytologic appearance.

The lesion was composed of spindloid and epitheloid cells with a high mitotic rate. Although most areas in the architectural pattern of cells were somewhat disorganized, in some areas there was a suggestion of interanastomosing fascicles of cells. Marked nuclear pleomorphism was present and occasional multinuclear cells were observed.

Immunohistochemical staining revealed that the specimen was negative for keratin, S-100 protein, and smooth muscle actin and strongly positive for vimentin. These immunochemical findings are consistent with sarcoma. Because smooth muscle actin was negative, leiomyosarcoma was highly unlikely. There was no evidence of calcification, which strongly indicated that the lesions were not granulomatous. Based on histology of the lesions and their multiplicity, MFH of metastatic origin was the most likely diagnosis. When sarcomatous primary lesions are occult, they are usually located in the retroperitoneum. The slides were reviewed by a second pathologist who concurred with the diagnosis.

The patient declined antineoplastic therapy and elected to be monitored clinically. Immediately after diagnosis with MFH, he gradually increased his intake of omega-3 fatty acids and eliminated vegetable oils from his diet, especially corn oil rich in the tumor-promoting fatty acid linoleic acid (LA; Table 1). His daily consumption was monitored for 10

Table 1. Dietary Supplementation Schedule of DH[a]

2 yr Prior to Diagnosis
Multivitamin/multimineral supplement (Theragran M, Walgreens Pharmaceutical, Deerfield, IL)
800 IU vitamin E (Nature Made, 400 IU, Mission Hills, CA)
1,000 mg vitamin C (Nature Made, 500 mg)
800 IU vitamin D (Citracal, 400 IU, Mission Pharmacal Co., Boerne, TX)
1,260 mg calcium (Citracal+D, 630 mg, Mission Pharmacal Co.)
1,000 mg glucosamine sulfate (Schiff, 1,000 mg, Salt Lake City, UT)
360 mg saw palmetto (True Nature, Inc., 160 mg, Naperville, IL)
81 mg aspirin (Kirkland, 81 mg, Quebec, Canada)
2,000 mg fish oil containing 240 mg DHA and 360 mg EPA (GNC fish oil,1,000 mg, Pittsburgh, PA)
Diagnosis, July 31, 2000
Gradually increased supplemental intake of omega-3 fatty acids and decreased omega-6 fatty acid intake by eliminating all vegetable oil from the diet with the exception of olive oil and canola oil, both low in omega-6 fatty acids and rich in omega-9 monounsaturated fatty acid
September 16, 2000
Consumed the following level of omega-3 fatty acid supplements
12 capsules of high-potency marine lipid concentrate containing 240 mg DHA and 360 mg EPA per capsule (Vitaline Corp., Ashland OR)
12 capsules of Neuromins 200 containing 200 mg DHA per capsule (Martek Biosciences, Columbia MD)
2,000 mg fish oil containing a total of 240 mg DHA and 360 mg EPA (GNC Fish Oil, 1,000 mg)
Total daily intake of omega-3 fatty acids
DHA 5,520 mg
EPA 4,680 mg
EPA+DHA 10,200 mg
July 30, 2001
Most tumors were visualized as being stable or shrinking, but one continued slow growth; omega-3 fatty acid intake was gradually increased to
19 capsules of high-potency marine lipid concentrate containing 240 mg DHA and 360 mg EPA per capsule (Vitaline Corp.)
18 capsules of Neuromins 200 containing 200 mg DHA per capsule (Martek Biosciences)
Total daily intake of omega-3 fatty acids
DHA 8,160 mg
EPA 6,840 mg
EPA+DHA 15,000 mg

a: Abbreviations are as follows: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid. This supplemental regimen of July 30, 2001, was maintained and continues through to the present.

Table 2. Daily Dietary Intake

Breakdown of Daily Kilocalories Consumed		
	Kilocalories	Percentage of Diet
Protein	404.1	17.8
Carbohydrate	1,077.6	47.6
Fat	763.3	34.6
Total	2,245	
Amounts of Specific Dietary Components		
Saturated fat		21.0 g
Monounsaturated fat		23.9 g
Oleic acid (C18:1n-9)		19.0 g
Polyunsaturated fat		17.2 g
Linoleic acid (C18:2n-6)		12.6 g
Linolenic acid (C18:3n-3)		1.6 g
Eicosapentaenoic acid (C20:5n-3)		0.2 g
Docosahexaenoic acid (C22:6n-3)		0.4 g
Cholesterol		305 mg
Vitamin E		10.7 IU
Vitamin A		15,300 IU
β-Carotene		3,839 IU
Vitamin D		26.1 IU
Vitamin C		280 mg
Calcium		510 mg

Table 3. Total Daily Intake of Omega-3 Fatty Acids

Sources and Amounts of Polyunsaturated Fatty Acids Consumed Daily		Dietary (mg)	Supplemental (mg)	Total (mg)
Omega-6 fatty acids				
	Linoleic acid	12,581	0	12,581
Omega-3 fatty acids				
	Linolenic acid	1,648	0	1,648
Long-chain omega-3 fatty acids				
	Eicosapentaenoic acid	161	6,840	7,001
	Docosahexaenoic acid	405	8,160	8,565
Long-chain omega-3 fatty acids total		566	15,000	15,566
Omega-3 fatty acids total		2,214	15,000	17,214
Ratio of Fatty Acids Consumed				
Linoleic acid/total omega-3 fatty acid		0.73		
Linoleic acid/total long-chain omega-3 fatty acids		0.81		
Linoleic acid/docosahexaenoic acid		1.47		

days, and his daily intake was estimated with the Nutritionist Pro program, version 1.3 (First Data Bank, San Bruno, CA). His estimated daily intake averaged 1,845 kcal/day, which was comprised of 17.8% protein, 47.6% carbohydrate, and 34.6% fat excluding his supplement (Table 2). By September 2000, his daily consumption of omega-3 fatty acids (diet + supplements) reached 12.4 g/day with the long-chain omega-3 fatty acid intake of 10.2 g/day (Table 1). He replaced the vegetable oils in his diet with olive oil or canola oil, rich in the monounsaturated fatty acid oleic acid, so his intake of saturated, monounsaturated, and PUFAs was 21.0, 23.9, and 17.2 g/day, respectfully (Table 2). It was reported by his physicians and himself that no other treatments were employed. He continued with clinical follow-up and by November 2000 had x-ray evidence of tumor shrinkage. Through 2001, the nodules continued to shrink with the exception of a nodule in his left mid-lung, which continually seemed to grow. A decision to biopsy the nonresponding lesion was made on August 23, 2001, and the repeat needle biopsy showed high-grade sarcoma similar to the previous biopsy of a different lesion. The patient remained asymptomatic and chose to avoid chemotherapy and continue on his nutritional program. Because one lesion continued to grow, he increased his intake of omega-3 fatty acids to 17.2 g/day, with an intake of long-chain omega-3 fatty acids of 15 g/day, and he remained on this regimen through to the present (Tables 1 and 3). The patient self-reported his daily intake of omega-3 fatty acids, which was verified by his

spouse and supported by his receipts from purchasing the omega-3 fatty acids. Furthermore, he reported that there were no other nutritional changes made except those mentioned for altering the lipid consumption. He tolerated this high dose of omega-3 fatty acid for over 3 yr, as he continually reported no adverse physical effects. Serial laboratory studies were performed (Table 4), and plasma hemogram, differential, metabolic, and lipid profiles were normal throughout the observation period with the exception that serum cholesterol (101–103 mg/dl), cholesterol/high-density lipoprotein (1.84–1.98), and low-density lipoprotein (40 mg/dl) were in the low range, and prothrombin time was found to be normal. A slight decrease in hematocrit was observed in June 2002 but was normal in the follow-up analysis 3 mo later. Since diagnosis, the patient has been periodically followed without conventional antineoplastic therapy. Serial CT scanning con-

Table 4. Medical Laboratory Values for DH[a]

Metabolic Profile Fasting		
Glucose	101–111 mg/dl	Normal
BUN	28 mg/dl	Normal
Creatinine	1.0–1.1 mg/dl	Normal
BUN/creatinine ratio	25.5	Normal
Calcium	9.4–9.7 mg/dl	Normal
Phosphorous	2.7 mg/dl	Normal
Total protein	6.9–7.5 g/dl	Normal
Albumin	4.0–4.6 g/dl	Normal
Globulin	2.3 g/dl	Normal
Albumin/globulin ratio	2.0	Normal
Total bilirubin	0.7–0.8 mg/dl	Normal
Alkaline phosphatase	41–54 IU/l	Normal
Aspartate amino transferase (SGOT)	24–29 IU/l	Normal
Alanine amino transferase (SGPT)	21–28 IU/l	Normal
Gamma glutamyl transpeptidase	26 IU/l	Normal
Sodium	138–141 meq/l	Normal
Potassium	4.0–4.3 meq/l	Normal
Chloride	101–103 meq/l	Normal
CO_2	25 meq/l	Normal
Hemogram		
WBC	6.2–7.1 1,000/mm^3	Normal
RBC	4.81–4.84 million/mm^3	Normal
Hemoglobin	14.7–15.3 g/dl	Normal
Hematocrit	43.4–45.3%	Normal
Mean cell volume	89.5–92.8 femptoliters	Normal
MCH	30.3–31.7 pg	Normal
MCH concentration	33–34.2%	Normal
Red cell distribution	13.1–13.6	Normal
Platelet count	218–297 1,000/mm^3	Normal
Mean platelet volume	8.3–8.8 femptoliters	Normal
Differential		
Segmented neutrophils	61.5–68.4%	Normal
Lymphocytes	22.7–27.8%	Low normal
Monocytes	5.1–6.8%	Normal
Eosinophils	3.5–3.6%	Normal
Basophils	0.3%	Normal
Lipid Panel		
Cholesterol	101–103 mg/dl	Low
Triglycerides	37–51 mg/dl	Normal
HDL	51–56 mg/dl	Normal
Very-low-density lipoprotein (calculated)	7– 10 mg/dl	Normal
Cholesterol/HDL ratio	1.84–1.98	Low
Low-density lipoprotein (calculated)	40 mg/dl	Low
Prothrombin time	12.6 s	Normal
International normalized ratio (INR)	1.1	Normal

a: Abbreviation are as follows: BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; and HDL, high-density lipoprotein. Blood analyses were evaluated periodically throughout the intervention; representative values are from August 20, 2001, November 9, 2001, September 22, 2003, and March 31, 2004.

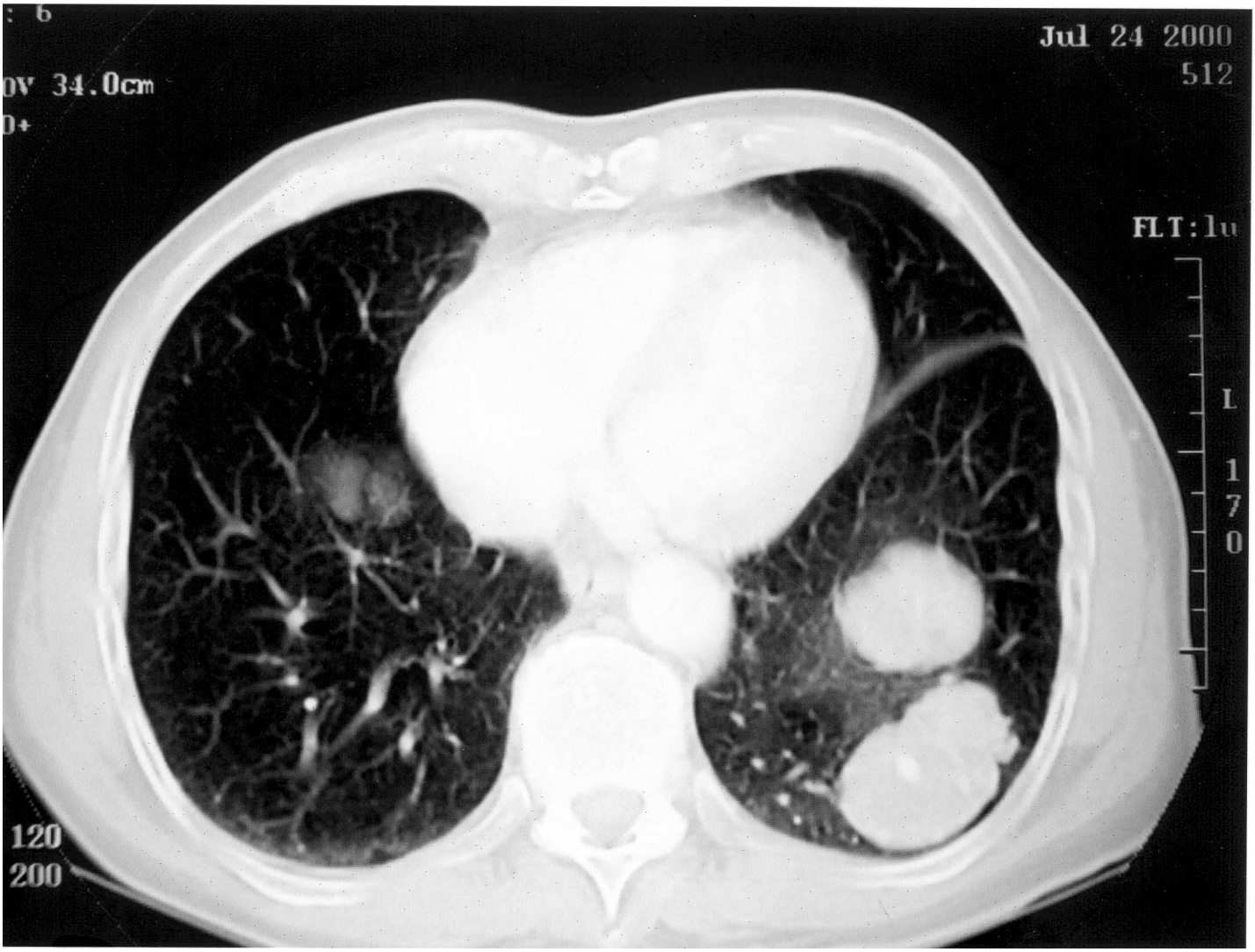

Figure 1. A: The initial computed tomography (CT) scan was performed on July 24, 2000. In the left lower lobe posterior basal segment two masses were found. The largest mass measured 5.0 × 3.6 cm and the other measured 3.8 × 3.4 cm.

tinues to demonstrate slow shrinkage of all pulmonary lesions (Fig. 1). The two large masses observed in the posterior basal segment were 18 and 12.9 cm^2 on July 24, 2000 (Fig. 1A), and decreased to 1.2 and 0.8 cm^2, respectively, by April 2, 2004 (Fig. 1B), representing a shrinkage of over 93% of both tumors. The large mass observed in the superior segment was 12.8 cm^2 on November 12, 2001 (Fig. 1C), and decreased to 2.6 cm^2 by April 2, 2004 (Fig. 1D), representing a shrinkage of 80% during the time period. His last scan was on April 2, 2004, and he remains without symptoms. Interestingly, during this period, he has had several non-melanoma cutaneous cancers removed surgically.

Discussion

The gradual and continual shrinkage of the pulmonary lesions observed with DH from July 2000 to April 2004 is attributed to the consumption of high quantities of the long-chain omega-3 fatty acids from fish oil and golden algae oil and the decreased consumption of vegetable oils rich in LA, considered to be a tumor-promoting fatty acid. This nutritional intervention/supplementation schedule (Tables 1 and 2) significantly altered the profile of fatty acids consumed by the patient (Table 3) and was the only change in lifestyle reported by DH.

In fact, the modern Western diet is considered to be deficient in omega-3 fatty acids and contains excessive amounts of omega-6 fatty acids, resulting in an omega-6/omega-3 essential fatty acid ratio of 15:1–16.7:1 (34). Several reports suggest that humans evolved from a diet comprised of a dietary ratio of omega-6/omega-3 fatty acids close to 1 (34). Because diets rich in omega-6 fatty acids, especially LA, have been reported to promote tumorigenesis (18–20) and diets rich in omega-3 fatty acids suppress tumorigenesis (13–26), the ratio of these essential fatty acids in the diet may be an important factor in the development and progression of various cancers. Indeed, the

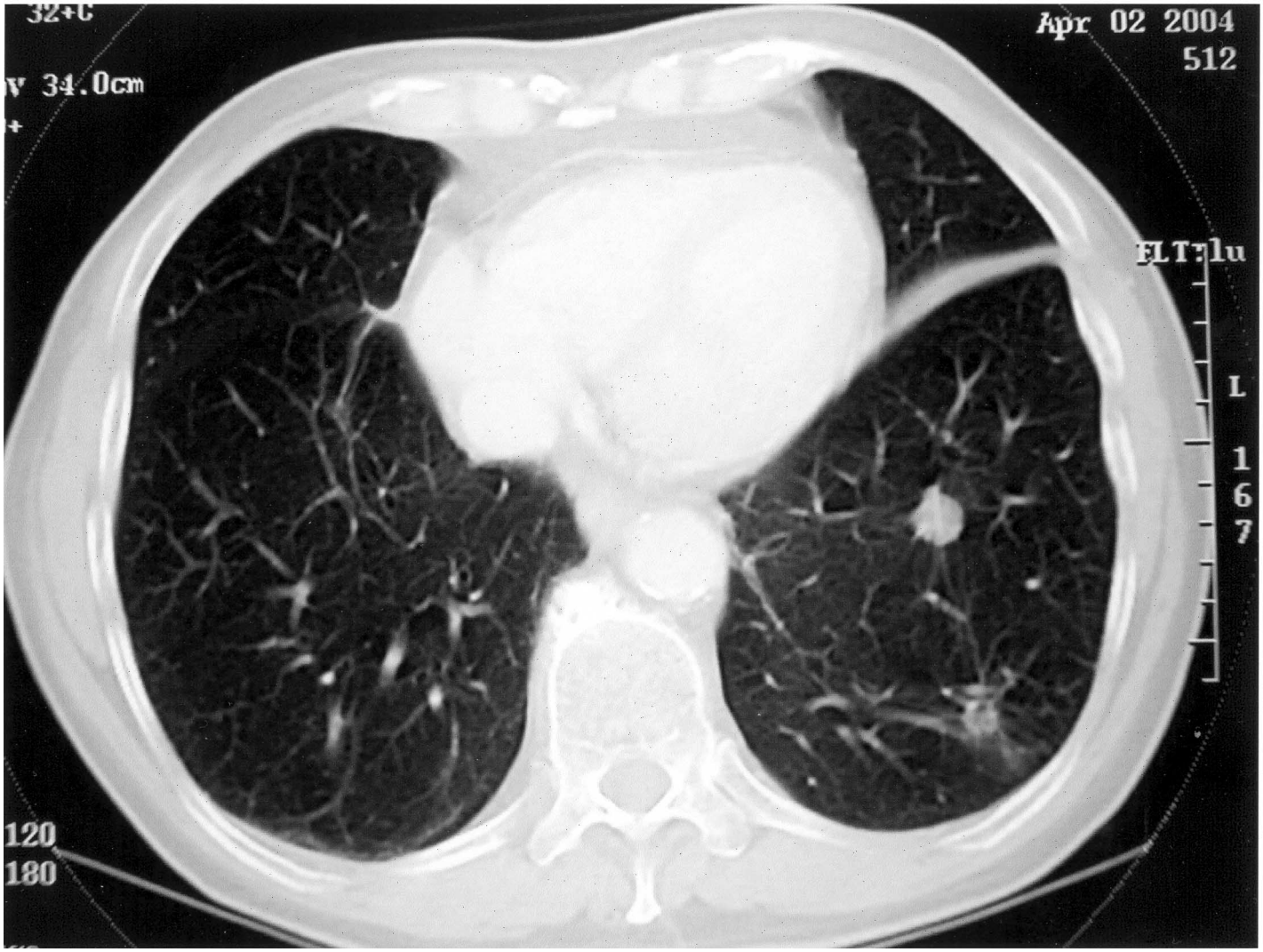

Figure 1. B: The most recent CT scan was performed on April 2, 2004. The two masses shown on the left lower lobe posterior segment (July 24, 2000) now measure 1.1 × 1.1 cm and 0.9 × 0.9 cm.

ratio of total omega-6 fatty acids to long-chain omega-3 fatty acids in adipose tissue was related to breast cancer risk in the EURAMIC multicenter study (11), a case-control study in Tours, France, that concluded that breast tissue omega-6/omega-3 fatty ratio is related to the risk of breast cancer (35), and breast tissue levels of omega-6 fatty acid may contribute to breast cancer, whereas omega-3 fatty acid levels may have a protective effect (36). Similar relationships were reported for prostate (37,38), colon (39), and squamous cell carcinoma of the skin (40).

It is important to note that the initial daily intake of the long-chain omega-3 PUFAs of 10.2 g/day (Table 1) was concomitant with the stabilization and gradual shrinkage of most tumors, but one tumor continued to slowly grow. When the long-chain omega-3 PUFA intake was increased to 15 g/day, shrinkage of the resistant lesion was observed. The observation that the single resistant lesion was sensitive to a higher dose of long-chain omega-3 PUFAs is suggestive of an omega-3 PUFA dose–response relationship. This supports the conclusion that omega-3 PUFA intake is associated with the shrinkage of the lung lesions seen in Fig. 1. At the lower dose, the DHA/LA ratio consumed per day was 2.1, but after increasing the omega-3 PUFA intake on July 30, 2001, the DHA/LA ratio decreased to 1.47 (Table 3); thus, it appears that a DHA/LA ratio below 1.5 was associated with the regression of all tumors in this single case.

It is noteworthy that DH consumed 15 g/day of omega-3 fatty acids since April 2, 2001, over 3 yr without symptomatic or laboratory side effects. In a phase I clinical trial, Burns et al. (41) reported that the mean tolerated dose of EPA+DHA was 13.1 g/day, a dose lower than that con-

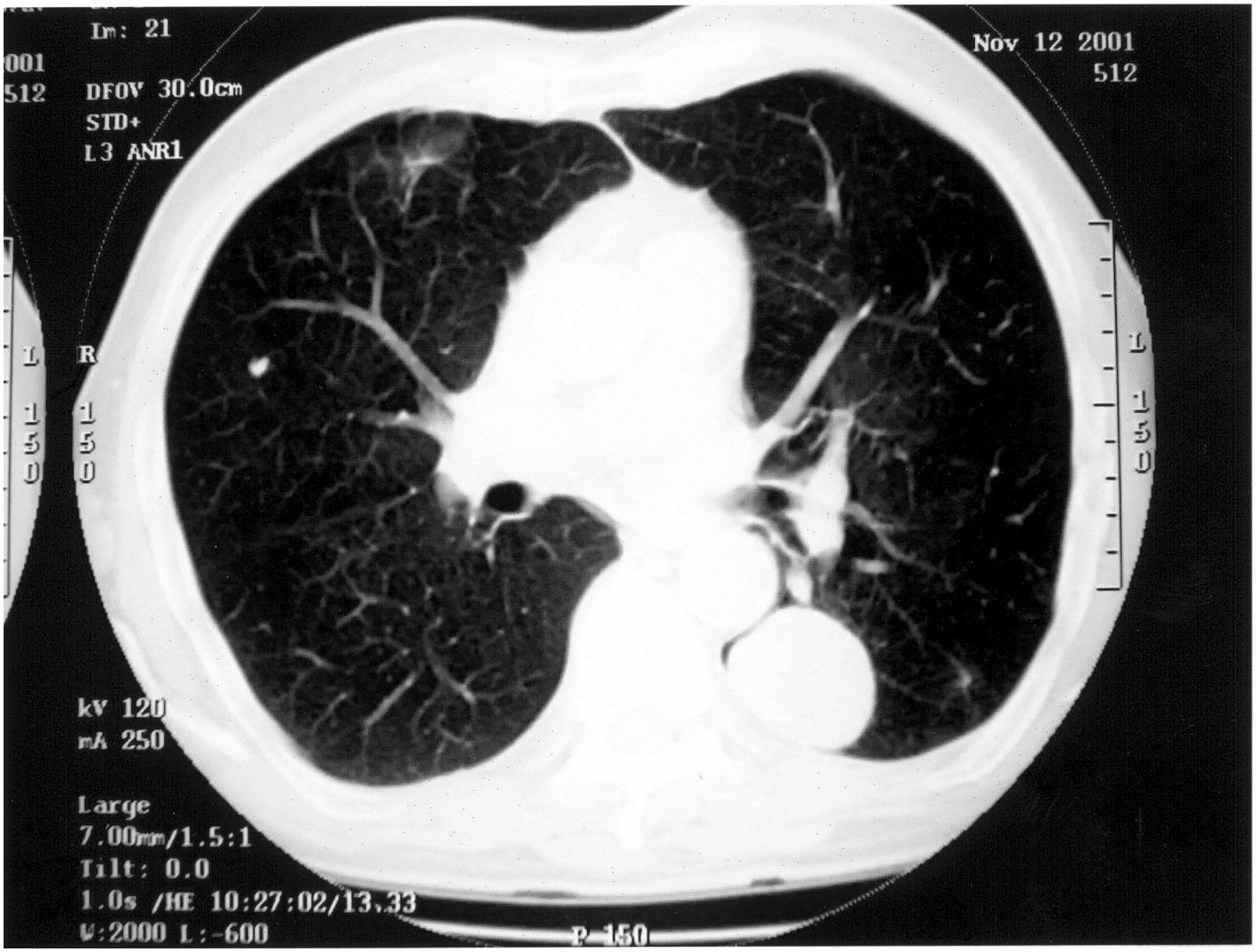

Figure 1. C: The CT scan dated November 12, 2001, demonstrated the a 4.0- × 3.2-cm mass in the superior segment of the left lower lobe.

sumed by DH. In addition, consumption of 10 g/day of EPA for 30 days (42) and 15 g/day of omega-3 fatty acids for 4 wk (43) was well tolerated in separate clinical trials. Krokan et al. (44) reported the consumption of 12 g EPA+DHA/day for 14 days without adverse side effects, and a series of studies in young healthy males consuming 6 g/day of DHA resulted in no observable physiological changes in blood coagulation, platelet function and thrombic tendencies (45), or lymphocyte function (46), and inhibition of natural killer cell activity was observed (47).

The LA/omega-3 fatty acid ratio consumed by DH during the period of observation was estimated to be 0.73, whereas the LA/DHA ratio was 1.47. This exceptionally low ratio of tumor-promoting omega-6 fatty acid (LA) to tumor-suppressing omega-3 fatty acid (DHA) may well be responsible for the bilateral decrease in tumor number and size observed with DH. This interesting observation that associates nutritional modification of the omega-6/omega-3 ratio consumed in the diet with the regression of malignant fibrous histiocytoma, a high-grade sarcoma with very poor prognosis and few conventional treatment options, warrants further rigorous scientific scrutiny in a broad-based clinical trial.

Until a more comprehensive clinical trial is performed we cannot recommend consumption of long-chain omega-3 PUFAs at the levels reported herein unless it is under the direction of a physician. The American Heart Association recommends consumption of 2–4 g of EPA+DHA per day in patients with elevated triglycerides. Furthermore, they recommend that this level would be difficult to obtain through consumption of fish alone and suggest that supplements could be taken under the consultation of a physician (48).

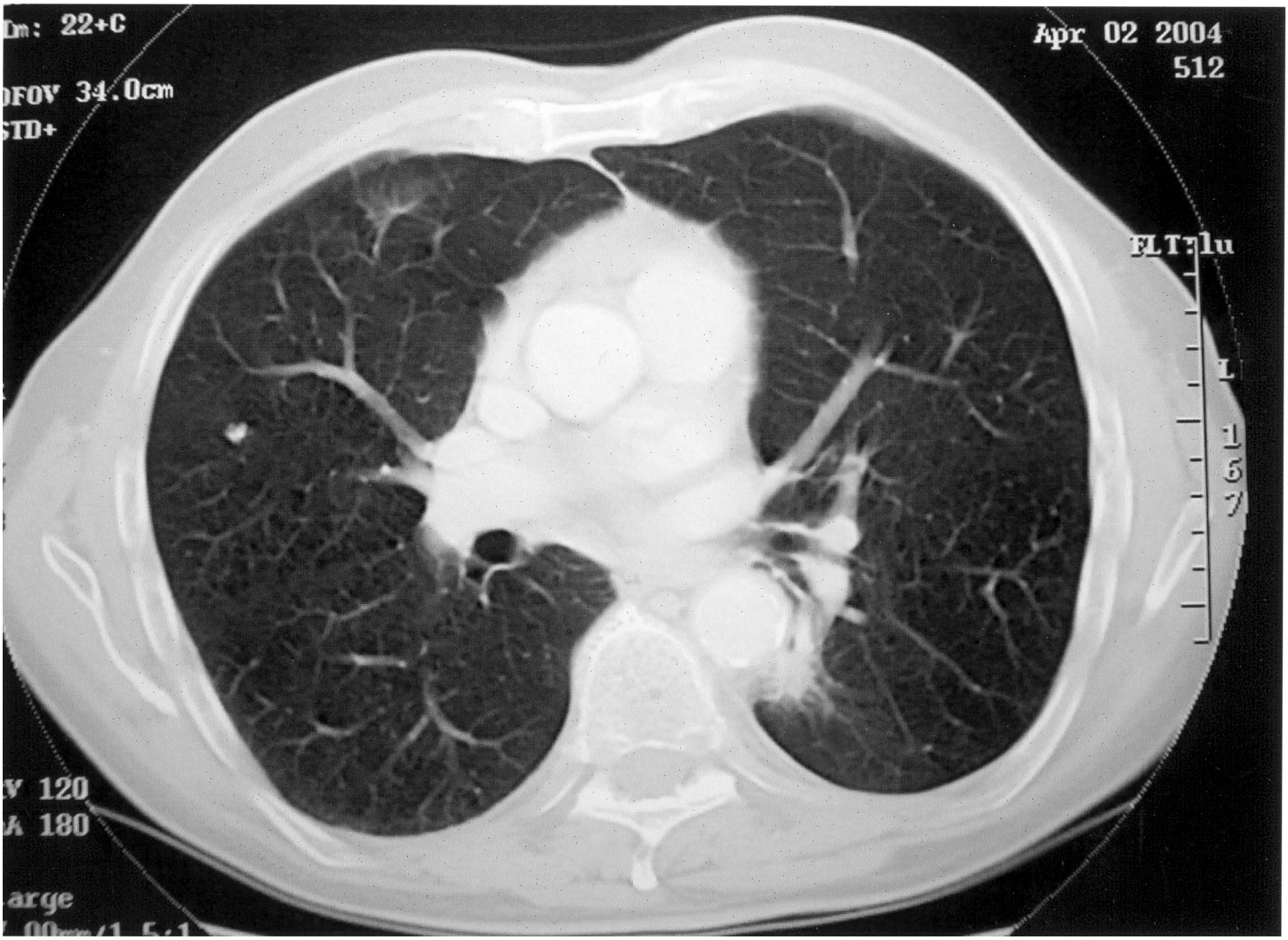

Figure 1. D: The follow-up CT of April 2, 2004, shows a significant decrease in the size of the mass shown in C in the superior segment of the lower left lobe. The mass now measures 1.2 × 2.2 cm.

Acknowledgments and Notes

Address correspondence to R. S. Pardini, Department of Biochemistry, College of Agriculture, Biotechnology and Natural Resources, University of Nevada, Reno, NV 89557. Phone: 775–784–6237. FAX: 775–784–6732. E-mail: ronp@cabnr.unr.edu.

Submitted 30 November 2004; accepted in final form 1 June 2005.

Reference

1. Gibbs JF, Huang PP, Lee RJ, McGrath B, Brooks J, et al.: Malignant fibrous histiocytoma: an institutional review. *Cancer Invest* **19,** 23–27, 2001.
2. Fujita Y, Shimizu T, Yamazaki K, Hirose T, Murayama M, et al.: Bronchial brushing cytology features of primary fibrous malignant histiocytoma of the lung. *Acta Cytol* **44,** 227–231, 2000.
3. Halyard MY, Camoriano JK, Culligan JA, Weiland LH, Allen MS, et al.: Malignant fibrous histiocytoma of the lung. Report of four cases and review of the literature. *Cancer* **78,** 2492–2497, 1996.
4. Bang HO, Dyerberg J, and Hjoorne N: The composition of food consumed by Greenland Eskimos. *Acta Med Scand* **200,** 69–73, 1976.
5. Blot WJ, Lanier A, Fraumeni JF, and Bender TR: Cancer mortality among Alaskan natives, 1960–1969. *JNCI* **55,** 547–554, 1975.
6. Caygill CP, Charlett A, and Hill MJ: Fat, fish, fish oil and cancer. *Br J Cancer* **74,** 159–164, 1996.
7. Bartsch H, Nair J, and Owen RW: Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: emerging evidence for their role as risk modifiers. *Carcinogenesis* **20,** 2209–2218, 1999.
8. Willet WC, Stampfer MJ, Colditz GA, Rosner BA, and Speizer FE: Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* **323,** 1664–1672, 1990.
9. Kazier L, Boyd NF, Kriukov V, and Tritchler D: Fish consumption and breast cancer risk: an ecological study. *Nutr Cancer* **12,** 61–68, 1989.
10. Sasaki S, Haracsek H, and Kestleloot H: An ecological study of the relationship between dietary fat intake and breast cancer mortality. *Prev Med* **22,** 187–202, 1993.
11. Simonsen N, van'tVeer P, Strain JJ, Martin-Moreno JM, Huttenen JK, et al.: 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. *Am J Epidemiol* **147,** 342–352, 1998.
12. Takezaki T, Inoue M, Kataoka H, Ikeda S, Yoshida M, et al.: Diet and lung cancer risk from a 14 year population based prospective study in Japan: with special reference to fish consumption. *Nutr Cancer* **45,** 160–167, 2003.

13. Karmali RA, Reichel P, Cohen LA, Terano T, Hiral A, et al.: Effects of dietary n-3 fatty acids on the DU-145 transplantable human prostate tumor. *Anticancer Res* **7,** 1173–1180, 1987.
14. Kort WJ, Weigma IM, Bijma AM, van Schalkwijk WP, Vergroesen AJ, et al.: Omega-3 fatty acids inhibit growth of transplantable mammary carcinoma. *JNCI* **79,** 593–599, 1987.
15. Borgeson CE, Pardini L, Pardini RS, and Reitz RC: Effects of dietary fish oil on human mammary carcinoma and on lipid metabolizing enzymes. *Lipids* **24,** 290–295, 1989.
16. Shao Y, Pardini L, and Pardini RS: Dietary menhaden oil enhances mitomycin C anti-tumor activity toward human mammary carcinoma MX-1. *Lipids* **30,** 1035–1045, 1995.
17. Shao Y, Pardini L, and Pardini RS: Intervention of transplantable human mammary carcinoma MX-1 chemotherapy with dietary menhaden oil in athymic mice: increased therapeutic effects and decreased toxicity of cyclophosphamide. *Nutr Cancer* **28,** 63–73, 1997.
18. Kato T, Hancock RL, Mohammadpour H, McGregor B, Manalo P, et al.: Influence of omega-3 fatty acids on the growth of human colon carcinoma in nude mice. *Cancer Lett* **187,** 169–177, 2002.
19. Rose DP, Connoly JM, Rayburn J, and Coleman M: Influence of diets containing eicosapentaenoic or docasahexaenoic acid on growth and metastasis of breast cancer cells in nude mice. *JNCI* **87,** 587–592, 1995.
20. Connoly JM, Gilhooly EM, and Rose DP: Effects of reduced dietary linoleic acid intake, alone or combined with an algal source of docosahexaenoic acid, on MDA-MB-231 breast cancer growth and apoptosis in nude mice. *Nutr Cancer* **35,** 44–49, 1999.
21. Reddy BS, Burill C, and Rigotti J: Effects of diets high in omega-3 and omega-6 fatty acids on initiation and postinitiation stages of colon carcinogenesis. *Cancer Res* **51,** 487–491, 1991.
22. Rose DP and Connolly JM: Omega-3 fatty acids as cancer chemoprevention agents. *Pharmacol Ther* **83,** 217–244, 1999.
23. Iigo M, Nakagawa T, Ishikawa C, Iwahori Y, Asamoto M, et al.: Inhibitory effects of docosahexaenoic acid on colon carcinoma 26 metastasis to the lung. *Br J Cancer* **75,** 650–655, 1997.
24. Chen ZY and Istfan NW: Docosahexaenoic acid is a potent inducer of apoptosis in HT-2 colon cancer cells. *Prostaglandins Leukot Essent Fatty Acids* **65,** 301–308, 2000.
25. Boudreau MC, Sohn KH, Rhee SH, Lee SW, Hunt JD, et al.: Suppression of tumor cell growth both in nude mice and in culture by n-3 polyunsaturated fatty acids: mediation through cyclooxygenase-independent pathways. *Cancer Res* **61,** 1386–1391, 2001.
26. Birt DF, White LT, Choi B, and Pelling JC: Dietary fat effects on the initiation and promotion of two-stage tumorigenesis in the SENCAR mouse. *Cancer Res* **49,** 4170–4174, 1989.
27. Kato T, Sorreta AG, Rivera G, Stafford J, and Pardini RS: Docosahexaenoic acid is the tumor suppressing fatty acid for human colon (WiDr, COLO 205) and prostate (PC-3, LNCaP) carcinomas. *Proc Am Assoc Cancer Res* **45**(3913), 309, 2004.
28. de Bravo MG, de Antueno RJ, Toledo J, De Tomas ME, Mercuri OF, et al.: Effects of an eicosapentaenoic and docosahexaenoic concentrate on a human lung carcinoma grown in nude mice. *Lipids* **26,** 866–870, 1991.
29. Maehle L, Lystad E, Eilertsen E, Einarsdottir E, Hostmark AT, et al.: Growth of human lung adenocarcinoma in nude mice is influenced by various types of dietary fat and vitamin E. *Anticancer Res* **19,** 1649–1655, 1999.
30. Booyens J, Engelbrecht P, le Roux S, Louwrens CC, Van der Merwe CF, et al.: Some effects of the essential fatty acids linolenic acid and alpha-linolenic acid and their metabolites gamma linolenic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid and of prostaglandins A1 E1 on the proliferation of human osteogenic sarcoma cells in culture. *Prostaglandins Leukot Med* **15,** 15–33, 1984.
31. Ramesh G and Das UN: Effect of cis-unsaturated fatty acids on meth-A ascitic tumour cells in vitro and in vivo. *Cancer Lett* **123,** 207–214, 1998.
32. Lopez CB, Barotto NN, Valentich MA, and Eynard AR: Morphological and biological characterization of two mesenchymal murine tumors and the modulation of their growth parameters by n-3 and n-6 polyunsaturated fatty acids. *Prostaglandins Leukot Essent Fatty Acids* **59,** 341–347, 1998.
33. Colquhoun A and Schumacher RI: Gamma-linolenic acid and eicosapentaenoic acid induce modifications in mitochondrial metabolism, reactive oxygen species, lipid peroxidation and apoptosis in Walker rat carcinosarcoma cells. *Biochem Biophys Acta* **1533,** 207–219, 2001.
34. Simopoulos AP: The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed Pharmacother* **56,** 365–379, 2002.
35. Maillard V, Bougnoux P, Ferrari P, Jourdan ML, Pinault M, et al.: n-3 and n-6 fatty acids in breast adipose tissue and relative risk of breast cancer in a case controlled study in Tours France. *Int J Cancer* **98,** 78–83, 2002.
36. Bragga D, Anders KH, Wang HJ, and Glaspy JA: Long-chain n-3 to n-6 polyunsaturated fatty acid ratios in breast adipose tissue from women with and without breast cancer. *Nutr Cancer* **42,** 180–185, 2002.
37. Yang YJ, Lee SH, Hong SJ, and Chung BC: Comparison of fatty acid profiles in the serum of patients with prostate cancer and benign prostatic hyperplasia. *Clin Biochem* **32,** 404–409, 1999.
38. Aronson WJ, Glaspy JA, Reddy ST, Reese D, Heber D, et al.: Modulation of omega-3/omega-6 polyunsaturated ratios with dietary fish oils in men with prostate cancer. *Urology* **58,** 283–288, 2001.
39. Huang YC, Jessup JM, Forse RA, Flickner S, Pleskow D, et al.: N-3 fatty acids decrease colonic epithelial cell proliferation in high-risk bowel mucosa. *Lipids* **31,** S313–S317, 1996.
40. Hakim IA, Harris RB, and Ritenbaugh C: Fat intake and risk of squamous cell carcinoma of the skin. *Nutr Cancer* **36,** 155–162, 2000.
41. Burns CP, Halabi S, Clamon GH, Hars V, Wagner BA, et al.: Phase I clinical study of fatty acid capsules for patients with cancer cachexia: cancer and leukemia group B study 9473. *Clin Cancer Res* **5,** 3942–3947, 1999.
42. Knapp HR, Reilly IA, Alessandrini P, and Fitzgerald GA: In vivo indexes of platelet and vascular function during fish oil administration in patients with atherosclerosis. *N Engl J Med* **314,** 937–942, 1986.
43. Knapp HR and Fitzgerald GA: The antihypertensive effects of fish oil. A controlled study of polyunsaturated fatty acid supplements in essential hypertension. *N Engl J Med* **320,** 1037–1043, 1989.
44. Krokan HE, Bjerve KS, and Mork E: The enteral bioavailability of eicosapentaenoic acid and docosahexaenoic acid is as good from ethyl esters as from glyceryl esters in spite of lower hydrolytic rates by pancreatic lipase in vitro. *Biochim Biophys Acta* **1168,** 59–67, 1993.
45. Nelson GJ, Schmidt PS, Bartolini GL, Kelley DS, and Kyle D: The effect of dietary docosahexaenoic acid on platelet function, platelet fatty acid composition and blood coagulation in humans. *Lipids* **32,** 1129–1136, 1997.
46. Kelley DS, Taylor PC, Nelson GC, and Mackey BE: Dietary docosahexaenoic acid and immunocompetence in young healthy men. *Lipids* **33,** 559–566, 1998.
47. Kelley DS, Taylor PC, Nelson GJ, Schmidt PC, Ferretti A, et al.: Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in healthy young men. *Lipids* **34,** 317–324, 1999.
48. Kris-Etherton PM, Harris WH, and Appel LJ: AHA scientific statement, fish consumption, fish oil, omega-3 fatty acids and cardiovascular disease. *Circulation* **106,** 2747–2757, 2002.