Dietary Omega-3 Polyunsaturated Fatty Acids plus Vitamin E Restore Immunodeficiency and Prolong Survival for Severely Ill Patients with Generalized Malignancy

A Randomized Control Trial

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BACKGROUND. The aim of the current prospective, randomized control study was to investigate the effect of dietary omega-3 polyunsaturated fatty acids plus vitamin E on the immune status and survival of well-nourished and malnourished patients with generalized malignancy.

METHODS. Sixty patients with generalized solid tumors were randomized to receive dietary supplementation with either fish oil (18 g of omega-3 polyunsaturated fatty acids, PUFA) or placebo daily until death. Each group included 15 well-nourished and 15 malnourished patients. The authors measured total T cells, T-helper cells, T-suppressor cells, natural killer cells, and the synthesis of interleukin-1, interleukin-6, and tumor necrosis factor by peripheral blood mononuclear cells before and on Day 40 of fish oil supplementation. Karnofsky performance status, nutritional state, and survival were also estimated.

RESULTS. The ratio of T-helper cells to T-suppressor cells was significantly lower in malnourished patients. Omega-3 PUFA had a considerable immunomodulating effect by increasing this ratio in the subgroup of malnourished patients. There were no significant differences in cytokine production among the various groups, except for a decrease in tumor necrosis factor production in malnourished cancer patients, which was restored by omega-3 fatty acids. The mean survival was significantly higher for the subgroup of well-nourished patients in both groups, whereas omega-3 fatty acids prolonged the survival of all the patients.

CONCLUSIONS. Malnutrition appears to be an important predictor of survival for patients with end stage malignant disease. Omega-3 polyunsaturated fatty acids had a significant immunomodulating effect and seemed to prolong the survival of malnourished patients with generalized malignancy. ***Cancer* 1998;82:395–402.**
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KEYWORDS: omega-3 polyunsaturated fatty acids, malnutrition, immunomodulation, survival, metastatic cancer.

In recent years, a large body of epidemiologic evidence demonstrated that diet and nutritional factors may be of major importance in the etiology of human cancer.[1–3] However, knowledge of the influence of nutritional support on tumor promotion remains insufficient.[4,5] On one hand, progressive anorexia, debilitation, and malnutrition in generalized malignancies seem to be immunosuppressive because they reduce the ability of the host's immune system to mobilize the various antitumor defense mechanisms.[6,7] On the other hand, administration

of nutritional support to the cancer patient may selectively feed the tumor and potentiate its growth.[8–10] These conflicting possibilities make the practice of nutrient administration to the cancer patient clinically controversial. It is highly possible that specific nutrients have different effects on tumor growth. In 1992, Istfam et al. proposed that this may happen through modulation of the transduction of second messenger signals and consequent changes in intracellular protein metabolism that could either enhance or reduce the proliferation potential of tumors.[11]

Both human epidemiologic surveys and animal studies have established that high fat diets are associated with a high incidence and accelerated development of certain tumors.[12–14] The connection between dietary fat and tumor promotion appears to be related, at least in part, to the influence of specific fatty acids on prostaglandin E2 production. It has been well documented that omega-6 polyunsaturated fatty acids may increase the production of the immunosuppressive prostaglandin E2 through the arachidonic acid pathway. Several studies have shown that eicosanoids may play a significant role in carcinogenesis,[15] whereas other evidence documents that prostaglandins can influence the proliferation of several cell lines.[16,17]

Because of the ability of omega-3 polyunsaturated fatty acids (PUFA/fish oil) to decrease prostaglandin E2 synthesis, several investigators have studied their effects on tumor growth and metastasis in laboratory animals. In summary, several recent reports have described the beneficial effects of dietary omega-3 fatty acids in reducing the incidence of carcinogen-induced tumors and also in reducing tumor growth rates and metastatic spread in animal models.[18–20] The abovementioned effects of dietary omega-3 PUFA may be the results of the enhancement of both defense mechanisms against tumor cells and tumor cell susceptibility via changes in cell membrane composition. Finally, dietary fish oil directly reduces tumor cell proliferation via alteration in prostaglandin metabolism.

In the current study, we investigated the effect of dietary supplementation with omega-3 PUFA plus vitamin E (vit E) as antioxidant on T-cell subsets and cytokine production in cancer patients who were or were not in a severely compromised nutritional state. We also tried to demonstrate the potential effect of fish oil on the patients' survival.

PATIENTS AND METHODS

Patients

A total of 64 patients in the Oncology Unit of the Department of Medicine, Patras University Medical School, with generalized solid tumors were randomized into the trial. None of our patients were under chemotherapeutic or immunomodulating treatment during the previous 4 months, and when the trial began no other efficient or established tumor treatment would be available to them. Four patients subsequently dropped from the study because of poor compliance, leaving 60 patients evaluable for response.

Our patients were randomized to receive 18 g of fish oil (6 capsules of MAXEPA 3 times daily containing 170 mg eicosapentanoic acid [EPA] and 115 mg docosahexanoic acid [DHA] per capsule) (Group A) or placebo (sugar tablets) (Group B). This dosage of omega-3 PUFA has previously been reported to exhibit a potent immunomodulating effect while being well tolerated by patients.[21] Patients in Group A also received 200 mg of vitamin E daily to compensate for the oxidative effect of omega-3 PUFA. Each group was divided into the following two subgroups: Group WN, which included patients in a good nutritional state (weight loss $<10\%$ during the last 6 months, serum albumin >30 g/L, serum transferrin >2.0 g/L, and Karnofsky performance status >60), and Group MN, which included patients with malnutrition (weight loss $>10\%$ during the last 6 months, serum albumin <30 g/L, serum transferrin <2.0 g/L, and Karnofsky performance status <60). A group of 15 healthy individuals served as controls. Written informed consent was obtained from all the patients involved in the study.

Our patients' characteristics (age, gender, tumor stage, and earlier treatment) are shown in Table 1.

T-Cell Measurement

Lymphocytes were separated from heparinized whole blood by Ficoll–Hypaque gradient sedimentation. T-cell phenotype was characterized by using monoclonal antibodies to total T cells, CD3 (anti-Leu 1 [Becton-Dickenson, San Jose, CA]), helper T cells, CD4 (anti-Leu 3_a [Becton-Dickenson] or OKT-4 [Ortho Pharmaceuticals]), suppressor T cells, CD8 (anti-Leu 2_a [Becton-Dickenson] or OKT-8 [Ortho Pharmaceuticals]) and natural killer (NK) cells (anti-Leu 11_b, CD16 [Becton-Dickenson]). Cell numbers were analyzed by indirect immunofluorescence microscopy. We calculated both the percentages and the absolute numbers of T-cell subsets.

In Vitro Stimulation of Mononuclear Cells

The mononuclear cell fraction was suspended at a concentration of 5×10^6 cells/mL in RPMI-1640 medium and stimulated with endotoxin (lipopolysaccharide *Escherichia coli* 055:B5, Sigma, St. Louis, MO) at 10 ng/mL. After incubation for 24 hours at 37 °C in 5% CO_2, the supernatants were removed from 96-well flat bottom microtiter plates and frozen at −70 °C, for

TABLE 1
Patient's Characteristics

	Group A (n = 30)		Group B (n = 30)	
Characteristic	**WN_A (n = 15)**	**MN_A (n = 15)**	**WN_B (n = 15)**	**MN_B (n = 15)**
Tumor type				
Breast	3	3	4	3
Gastrointestinal	6	4	6	5
Lung	2	3	2	4
Liver	2	2	1	2
Pancreas	2	3	2	1
Tumor stage				
Pulmonary metastasis	7	6	4	3
Liver metastasis	9	9	10	7
Peritoneal metastasis	3	5	4	5
Bone metastasis	10	8	8	7
Earlier treatment				
Surgery	11	9	10	8
Chemotherapy	9	8	11	8
Radiotherapy	2	1	1	2
None	3	3	1	3
Mean age (yrs)	58 ± 4	56 ± 3	60 ± 5	57 ± 4
Gender (male/female)	9/6	8/7	9/6	10/5
Serum albumin (g/L)	32.9 ± 0.8	26.7 ± 0.7	33.4 ± 0.9	25.4 ± 0.6
Karnofsky performance status	77 ± 4	51 ± 3	72 ± 5	54 ± 2
Weight loss (%)	6.7 ± 0.8	13.3 ± 0.7	5.8 ± 0.7	14.6 ± 2.1

Group A: patients receiving omega-3 polyunsaturated fatty acids plus vitamin E; Group B: patients on a placebo diet; WN: well-nourished patients; MN: malnourished patients.

future determination of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF).

Cytokine Determination

IL-1, IL-6, and TNF synthesis were measured by using an enzyme-linked immunosorbent assay (ELISA) kit (Medgenix, Medgenix Diagnostics, Belgium).

All the above immunologic parameters were measured before and on Day 40 during dietary supplementation with omega-3 PUFA or placebo in all study groups. This time interval was necessary for a significant increase in eicosapentanoic acid concentration of mononuclear cell phospholipid fatty acids in patients treated with omega-3 PUFA.[22] We also measured T-cell subsets and cytokine production, one time each, in the healthy controls group.

Statistical Analysis

The Kolmogorov–Smirnov goodness of fit test was used to check all the data as well as the subpopulations for parametric distributions. To assess the statistical significance of the observed difference among continuous values, we adopted the one-way ANOVA. In our effort to determine the groups that really differed, we used the unpaired Student's *t*-test or its nonparametric equivalent, the Mann–Whitney *U* test.

For comparisons of data from the same group of patients but from different time intervals, we used repeated measures analysis of variance; and for the pairwise comparisons, we used paired *t* test (or Wilcoxon's signed rank tests when the data did not follow the normal distribution).

Survival was estimated by using life table analysis, and differences in survival were tested by the Mantel–Haenszel chi-square test.

RESULTS

The aims of our study were 1) to investigate the impact of the nutritional state on the immune response and survival of patients with generalized malignancy and 2) to evaluate the significance of dietary omega-3 PUFA supplementation for immunomodulation and survival, especially in the subgroup of the mostly immunocompromised, severely malnourished cancer patients.

T-Cell Subsets

We observed a significant ($P < 0.05$) decrease in both the absolute numbers and the percentages of total T

TABLE 2
Percentages of T-Cell Subsets before and during Omega-3 PUFA Supplementation (± Standard Deviation)

	WN_A group	MN_A group	WN_B group	MN_B group	C group
CD3					
Before	62.5 ± 15.1[a]	46.6 ± 11.5[b]	59.8 ± 11.7[a]	40.4 ± 9.8[b]	65.3 ± 14.6[c]
Day 40	60.6 ± 12.8	59.5 ± 12.7	56.9 ± 14.1	37.3 ± 10.2	
CD4					
Before	38.5 ± 10.7[a']	28.7 ± 9.4[b']	40.1 ± 11.2[a']	26.2 ± 9.7[b']	44.7 ± 10.8[c']
Day 40	37.6 ± 9.9	39.7 ± 11.2	39.3 ± 10.1	24.7 ± 8.9	
CD8					
Before	22.2 ± 7.1	28.8 ± 7.5	21.7 ± 6.9	24.5 ± 6.9	20.1 ± 8.7
Day 40	18.7 ± 6.2	18.9 ± 7.5	20.2 ± 7.4	22.8 ± 7.1	
CD4/CD8					
Before	1.75 ± 0.30[d]	1.21 ± 0.26[e]	1.82 ± 0.33[d]	1.23 ± 0.18[e]	2.17 ± 0.51[f]
Day 40	2.03 ± 0.45[d']	1.84 ± 0.40[e']	1.79 ± 0.34	1.19 ± 0.22	
NK cells					
Before	10.8 ± 2.3	11.4 ± 3.3	13.2 ± 3.1	14.2 ± 4.7	13.2 ± 3.9
Day 40	12.7 ± 3.0	13.3 ± 4.5	14.1 ± 2.9	10.9 ± 3.6	

PUFA: polyunsaturated fatty acids; WN_A group: well-nourished patients receiving omega-3 PUFA plus vitamin E; MN_A group: malnourished patients receiving omega-3 PUFA plus vitamin E; WN_B group: well-nourished patients receiving a placebo diet; MN_B group: malnourished patients receiving a placebo diet; C group: healthy controls; CD3: total T cells, CD4: helper T cells, CD8: suppressor T cells; NK cells: natural killer cells.

[a-b] $P < 0.05$.
[c-b] $P < 0.05$.
[a'-b'] $P < 0.05$.
[c'-b'] $P < 0.05$.
[d-e] $P < 0.01$.
[f-e] $P < 0.01$.
[e-e'] $P < 0.05$.

cells and helper T cells in the subgroup of the malnourished patients (MN) compared with controls (C) and well-nourished patients (WN) in both groups (Tables 2 and 3). Suppressor T cells were not significantly affected. This resulted in a significant decrease of the helper/suppressor T-cell ratio (Th/Ts) in both the MN groups compared with WN groups and healthy controls ($P < 0.05$). A very noteworthy finding was that omega-3 PUFA supplementation restored the low Th/Ts ratio in the peripheral blood of the malnourished cancer patients (Group MN_A), whereas this did not happen in the placebo group (Group MN_B) [Table 2, Fig. 1]. This was the result of a significant increase in the absolute number and percentage of helper T cells and a decrease in suppressor T cells in Group MN_A ($P < 0.05$). An increase in the Th/Ts ratio was also noted in the group of well-nourished patients who received omega-3 PUFA (Group WN_A), but the increase did not reach a statistically significant level ($P = 0.07$).

Cytokine Production

We measured serum IL-1, IL-6, and TNF levels, as well as IL-1, IL-6 and TNF production, by peripheral blood mononuclear cells (PBMC). TNF and IL-1 detection in the circulation was only sporadic, whereas low levels of IL-6 (<100 pg/mL) were detected in almost all our patients. It was not possible to demonstrate any significant differences in serum cytokines in any patient group.

TNF synthesis by PBMC stimulated in vitro by endotoxin was significantly ($P < 0.001$) lower in malnourished cancer patients than in those with a good nutritional status, whereas no significant differences were detected in IL-1 and IL-6 production. Omega-3 supplementation resulted in a significant ($P < 0.05$) increase in TNF production by PBMC of malnourished patients, and the values afterwards were not different from those for the well-nourished patients. No significant effects were shown on the production of either IL-1 or IL-6. The effects of omega-3 PUFA on cytokine synthesis in the various study groups are shown in Table 4.

Finally, no statistically significant differences were observed in either T-cell subsets or cytokine production in the group of patients under placebo diet before and on Day 40 (Tables 2–4).

Nutritional Response

There was no effect of omega-3 PUFA on body weight, serum albumin, or serum transferrin in either group.

TABLE 3
Absolute Numbers of T-Cell Subsets before and during Omega-3 PUFA Supplementation (± Standard Deviation)

	WN_A group	MN_A group	WN_B group	MN_B group	C group
CD3					
Before	1431 ± 346[a]	1005 ± 248[b]	1387 ± 285[a]	972 ± 186[b]	1575 ± 352[c]
Day 40	1418 ± 299	1341 ± 286	1195 ± 315	895 ± 207	
CD4					
Before	881 ± 244[a']	619 ± 202[b']	954 ± 216[a']	664 ± 162[b']	1078 ± 260[c']
Day 40	880 ± 231	835 ± 235	859 ± 308	590 ± 199	
CD8					
Before	508 ± 162	598 ± 155[d]	533 ± 181	547 ± 125	484 ± 209
Day 40	437 ± 145	382 ± 151	529 ± 214	504 ± 172	
NK cells					
Before	247 ± 53	237 ± 68	326 ± 61	411 ± 92	318 ± 94
Day 40	296 ± 70	251 ± 85	351 ± 68	223 ± 112	

PUFA: polyunsaturated fatty acids; WN_A group: well-nourished patients receiving omega-3 PUFA plus vitamin E; MN_A group: malnourished patients receiving omega-3 PUFA plus vitamin E; WN_B group: well-nourished patients receiving a placebo diet; MN_B group: malnourished patients receiving a placebo diet; C group: healthy controls; CD3: total T cells; CD4: helper T cells; CD8: suppressor T cells; NK cells: natural killer cells.

[a-b] $P < 0.05$.

[c-b] $P < 0.05$.

[a'-b'] $P < 0.05$.

[c'-b'] $P < 0.05$.

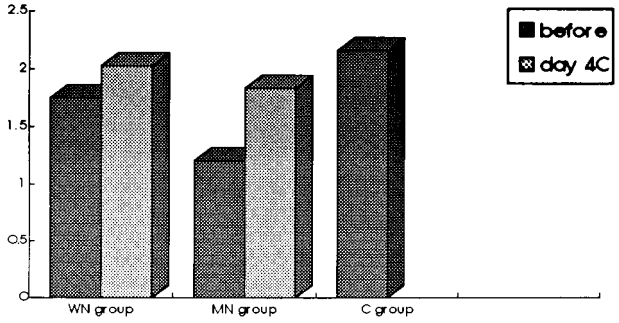

FIGURE 1. T-helper/T-suppressor cell ratio is shown before and on Day 40 during dietary supplementation with fish oil given to well-nourished patients (WN group), malnourished patients (MN group), and controls (C group).

However, we detected a significant increase in Karnofsky performance status[22] from 51 ± 3 to 72 ± 4 in the group of malnourished patients 40 days during omega-3 supplementation ($P < 0.01$).

Survival

We observed significantly ($P < 0.001$) prolonged survival among well-nourished compared with malnourished patients (Fig. 2). In the survival curves of Figure 3, it is demonstrated that the best survival was noted for the group of well-nourished patients treated with omega-3 PUFA plus vit E and the worst survival in malnourished patients on the placebo diet. The most noteworthy finding, however, was that omega-3 PUFA plus vit E dietary supplementation resulted in a significant ($P < 0.025$) increase in survival for all patients compared with the placebo group (Fig. 4). No differences were noted regarding days of hospitalization or infectious complications among the study groups.

Finally, no serious toxicity was observed in our patients, except for mild abdominal discomfort and transient diarrhea.

Discussion

Generalized malignancy due to solid tumors is a perplexing clinical problem with various medical, social, and even economic aspects. Although modern chemotherapeutic regimens have appeared, there was no progress to improve the quality of life and survival of patients with end stage cancer. Therefore, it would be interesting to consider alternative, less toxic treatment approaches based on our better understanding of cancer immunobiology and the immunologic interactions between tumor and host.

Tumor cell proliferation, metastatic disease, and tumor-host interaction seem to be mediated by a complexity of interactions among the immune system (mainly cytokines, T cells, and natural killer cells), growth factors, and classic hormones.[23,24] Prostaglandins, mainly PGE_2, which have an active role in cell proliferative processes in a variety of tissues, may also play a role in tumor growth. They seem to be important factors in the cascades that determine the bal-

TABLE 4
Cytokine Production (pg/mL) by Endotoxin-Stimulated Peripheral Blood Mononuclear Cells (± Standard Deviation)

	WN_A group	MN_A group	WN_B group	MN_B group	C group
IL-1					
Before	1810 ± 180	2160 ± 510	1685 ± 236	1894 ± 332	2087 ± 164
Day 40	1720 ± 50	3540 ± 730	2150 ± 144	2730 ± 98	
IL-6					
Before	2089 ± 178	2056 ± 264	2340 ± 328	1943 ± 165	2376 ± 163
Day 40	1818 ± 197	1998 ± 87	1976 ± 181	2117 ± 133	
TNF-α					
Before	778[a] ± 88	369[b] ± 32	813[a] ± 135[a]	578[b] ± 54	823 ± 71
Day 40	1139[c] ± 186	784[d] ± 207	756 ± 206	492 ± 154	

PUFA: polyunsaturated fatty acids; WN_A group: well-nourished patients receiving omega-3 PUFA plus vitamin E; MN_A group: malnourished patients receiving omega-3 PUFA plus vitamin E; WN_B group: well-nourished patients receiving a placebo diet; MN_B group: malnourished patients receiving a placebo diet; IL-1: interleukin-1; IL-2: interleukin-2; TNF: tumor necrosis factor; NS: not significant.
[a-b] $P < 0.001$.
[b-d] $P < 0.05$.
[c-d] N.S.
[a-c] N.S.

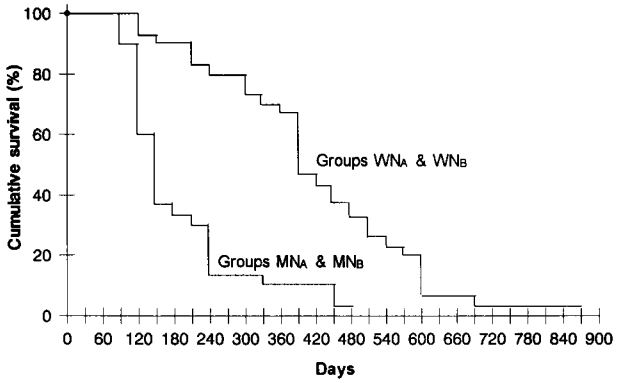

FIGURE 2. Cumulative survival is shown for well-nourished (Groups $WN_A + WN_B$) versus malnourished (Groups $MN_A + MN_B$) patients. The survival was significantly prolonged ($P < 0.001$) for well-nourished patients.

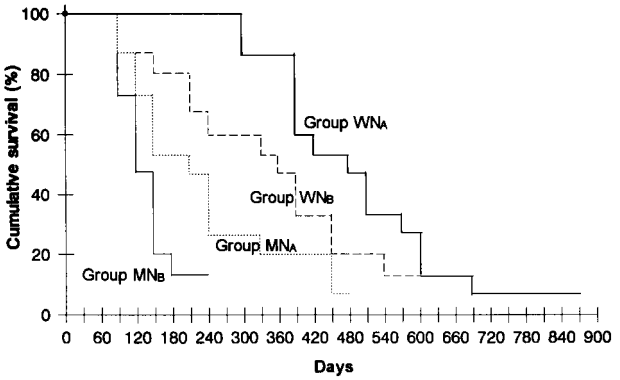

FIGURE 3. Survival curves are shown for all patient groups (WN_A: well-nourished patients receiving omega-3 polyunsaturated fatty acids (PUFA) plus vitamin E; WN_B: well-nourished patients receiving a placebo diet; MN_A: malnourished patients receiving omega-3 PUFA plus vitamin E; MN_B: malnourished patients receiving a placebo diet. There was a significant difference ($P < 0.05$) among all groups.

ance between growth arrest and tumor progression in experimental and clinical studies of cancer.[25] Cancer cachexia (e.g., inanition, anorexia, weakness, tissue wasting, and organ dysfunction in patients with cancer) seems to be a major factor contributing to the weakening of the already compromised immune system of the cancer patient. Cancer cachexia affects nearly 50% of cancer patients at the time of diagnosis and appears to influence outcome adversely. A current belief is that the mechanism of cancer cachexia involves the host's production of certain cytokines, such as IL-1, IL-6, TNF, and interferon gamma (IFN-γ), and perhaps additional factors, such as D-factor or a recently characterized wasting factor, 24K proteoglycan.[26]

Thus, a major clinical question is whether new treatment strategies based on immunologic approaches, prostaglandin interventions, or anticachexia treatment might improve life expectancy and quality of life for cachectic patients with advanced cancer.

In the current study, we tried to evaluate the effect of dietary supplementation with omega-3 PUFA on the immune status and survival of patients with generalized malignancy. We detected that malnutrition is a major factor contributing to morbidity in cancer patients, as the mean survival of malnourished patients was 213 ± 19 days compared with 481 ± 35 days for well-nourished patients. The relatively long survival of

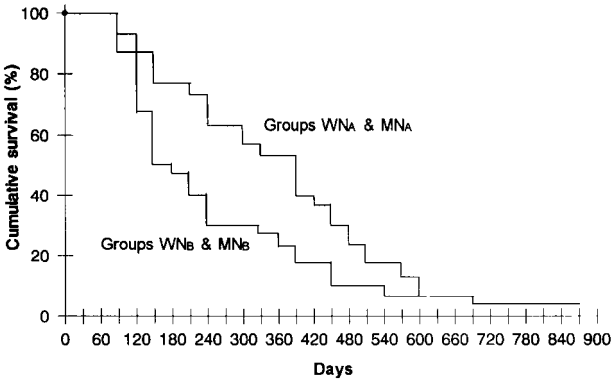

FIGURE 4. Survival curves are shown from a curve analysis of pooled patients receiving omega-3 polyunsaturated fatty acids (PUFA) plus vitamin E (groups $WN_A + MN_A$) or a placebo diet ($WN_B + MN_B$). The survival was significantly longer for patients receiving omega-3 PUFA ($P < 0.025$).

the WN_B group seems to be the result of both the absence of cachexia (body weight, serum albumin, and Karnofsky performance status near normal) and the presence of a proper immune response. We observed an inverse relationship between the nutritional state of patients with advanced cancer and the T-helper/T-suppressor cell ratio and the capacity of peripheral blood mononuclear cells (PBMC) to synthesize TNF-α in vitro. Our findings were similar to those of Aderka et al., who showed that patients with advanced cancer disease and extensive metastases had lower in vitro lipopolysaccharide (LPS)-induced TNF-α production than individuals with more limited disease.[27] Dietary supplementation with omega-3 PUFA (18 g/day) restored both the Th/Ts cell ratio and TNF production by endotoxin-stimulated PBMC. Our finding is not in accordance with former reports that long term consumption of omega-3 PUFA decreases T cell mitogenic response, DTH, and the percentage of T-helper cells,[28] and this may be the result of the parallel antioxidant effect of vit E. Most significantly, omega-3 PUFA increased the survival of all our patients, whereas the good nutritional state seems to influence the very long median survival for the WNA group. However, both omega-3 PUFA and nutritional state seem to be independent prognostic factors for survival, as we detected a statistically significant difference ($P < 0.05$) between the survival curves of Groups WN_A and WN_B (Fig. 3).

A link between dietary fat and cancer has long been established, mainly through epidemiologic data, whereas more recent work with laboratory animals has further strengthened the association of dietary fat with tumor growth and metastasis.[29,30] A beneficial effect of dietary omega-3 PUFA on tumor growth has been well documented by several animal studies,[31] and reversal of cachexia by EPA in a mouse model was recently described.[32] Our results demonstrate for the first time that high doses of dietary omega-3 PUFA (18 g/day), given in parallel with antioxidant supplementation, may prolong the survival of patients with generalized malignancy. We also noted an immunorestorative effect of fish oil through a significant increase of Th/Ts cell ratio and TNF-α production by PBMC in malnourished patients with advanced cancer.

The effects of omega-3 PUFA on the phospholipid fraction of the immune cell population, alteration in membrane structure, and changes in cellular signal transduction that influence growth and proliferation may be possible mechanisms of tumor growth inhibition by fish oil.[33] However, the main antitumor effect of fish oil seems to be the result of a direct reduction of tumor cell proliferation through reduction of the tissue levels of prostaglandin E_2 and its metabolites. It is well documented that dietary supplementation with omega-3 PUFA decreases prostaglandin E_2 release by in vitro stimulated PBMC,[21] and eicosanoids seem to play a significant role in carcinogenesis.[15] In 1994, Lundholm et al. demonstrated that prostaglandin synthesis inhibition via anti-inflammatory treatment may prolong the survival of patients with solid advanced cancer.[34] Similarly, a recent study by Wigmore et al. suggested that fish oil may temporarily stop the wasting process in cachectic patients with pancreatic carcinoma.[35]

We believe that dietary omega-3 PUFA, supplemented with an antioxidant such as vit E, may offer palliative support, mainly to undernourished patients with end stage metastatic disease, especially when it appears possible that no other chemotherapeutic approach will affect quality of life and survival. This may be the result of both their anticachectic and antitumor effects, through their action on eicosanoid synthesis and their unique immunomodulating effects. The observed suppressive effect of fish oil on cell-mediated immunity seems to be minimized by a parallel intake of an appropriate level of an antioxidant, such as vit E, without compromising its beneficial effects.

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