Fish Oil–Enriched Nutritional Supplement Attenuates Progression of the Acute-Phase Response in Weight-Losing Patients with Advanced Pancreatic Cancer[1,2]

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ABSTRACT The presence of an acute-phase protein response (APPR) has been suggested to shorten survival and contribute to weight loss in patients with pancreatic cancer. Fatty acids derived from fish oil have been shown to alter proinflammatory cytokine production and acute-phase protein synthesis in vitro. The present study was designed to determine the effects of a fish oil–enriched nutritional supplement on the concentrations of a range of individual acute-phase proteins (APP) in patients with advanced pancreatic cancer. In a sequential series, 18 patients with pancreatic cancer received the supplement (providing 2 g eicosapentaenoic acid and 1 g docosahexaenoic acid/d) for 3 wk while another 18 received full supportive care alone. Six healthy subjects served as additional controls. Acute-phase proteins were measured before and after the 3-wk intervention period in cancer patients. At baseline, albumin, transferrin and pre-albumin were significantly reduced and fibrinogen, haptoglobin, α-1-acid glycoprotein, α-1-antitrypsin, ceruloplasmin and C-reactive protein (CRP) were significantly elevated in the cancer patients compared with healthy controls, reflecting their roles as negative and positive acute phase proteins, respectively. In the supplemented cancer group, the only significant change in APP concentrations over the 4-wk study period was an increase in transferrin. In the control cancer group there were further significant reductions in albumin, transferrin and pre-albumin, and a significant increase in CRP concentration. These results suggest that many positive and negative APP are altered in advanced pancreatic cancer. The APPR tends to progress in untreated patients but may be stabilized by the administration of a fish oil–enriched nutritional supplement. This may have implications for reducing wasting in such patients. J. Nutr. 129: 1120–1125, 1999.

KEYWORDS: • *cancer cachexia* • *acute-phase protein response* • *fish oil* • *eicosapentaenoic acid* • *humans*

The acute-phase protein response (APPR)[4] is seen following a wide variety of insults to the body including trauma, infection, inflammation and cancer. C-reactive protein (CRP) is the archetypal positive acute-phase protein (APP) in humans (Baumann and Gauldie 1994) and is widely used as a marker for the acute-phase response (APR) in clinical practice. At diagnosis ~40% of patients with pancreatic cancer exhibit an elevated serum level of CRP. This proportion increases to ~80% as patients approach the time of death (Falconer et al. 1994). We have found the presence of an elevated CRP level to be an independent and robust predictor of poor survival in pancreatic cancer (Falconer et al. 1995).

In the human hepatocyte the production of APP is regulated by interleukin (IL)-6 (Castell et al. 1990). Thus the level of the APR in vivo may be taken as indirect evidence of proinflammatory cytokine production. From studies in animal models a variety of proinflammatory cytokines have been strongly implicated in both the anorexia and altered metabolism thought to contribute to cancer cachexia (Tracey et al. 1988, Yasumoto et al. 1995). However, it is not known whether the loss of lean tissue in cachexia is due to a direct effect of cytokines at the level of skeletal muscle or whether

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[4] Abbreviations used: APP, acute phase protein; APPR, acute phase protein response; APR, acute-phase response; CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IL, interleukin.

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TABLE 1

Characteristics of cancer patients and healthy controls

				UICC disease stage[2]		
	n	Age	Prestudy weight loss	2	3	4
		y	%			
Cancer patients receiving fish oil-enriched supplement	18	64[1] (56–66)	17.9 (15.9–20.7)	8	2	8
Cancer patients receiving supportive care	18	60 (54–70)	11.8 (5.6–23.5)	10	2	6
Healthy controls	6	54[3] (50–56)	0		—	

[1] Values are median (interquartile range).
[2] Hermreck et al. 1974.
[3] $P = 0.017$ between all cancer patients and healthy controls by Mann Whitney U test.

net loss of muscle protein is due to indirect effects of altered metabolism elsewhere, or a combination of these two.

It has been suggested that with the induction of APR during inadequate dietary intake, the imbalance in amino acid composition between skeletal muscle and APP may contribute to increased loss of muscle (Reeds et al. 1994). Clearly, for this mechanism to be important, there would have to be a uniform upregulation of the positive APP whose serum concentrations are measured in gram quantities and have a high turnover rate. However, there is little information on the range of APP that are upregulated in cachectic cancer patients.

Cancer cachexia has proven resistant to intervention with supplemental enteral or parenteral nutrition (Nixon et al. 1981, Ovesen et al. 1993). This may be due to metabolic changes, including the APPR, which at least in part, are stimulated by increased tumor or host production of proinflammatory cytokines (Castell et al. 1990, Falconer et al. 1994, Strassmann et al. 1993, Yasumoto et al. 1995). We have previously shown that fish oil or eicosapentaenoic acid (EPA), a polyunsaturated fatty acid derived from fish oil, administered to patients with advanced pancreatic cancer may attenuate weight loss while down-regulating production of IL-6 and serum levels of CRP (Wigmore et al. 1996, Wigmore et al. 1997a). Although in vitro work has suggested that EPA may have differential effects on a spectrum of acute phase proteins produced in response to IL-6 (Wigmore et al. 1997b), it is not known what effect EPA has on the concentration of a range of APP when it is administered in vivo.

This study was designed to determine the effects of the administration of a nutritional supplement containing EPA-rich fish oil on the levels of individual APP in patients with advanced pancreatic cancer compared with patients receiving full supportive care alone.

METHODS

Subjects. After informed consent and local ethical committee approval, 36 weight-losing patients with advanced pancreatic cancer were studied and compared with 6 healthy individuals. Diagnosis of advanced pancreatic cancer was based on histologic or unequivocal radiology or operative findings. Weight was measured with subject in light clothing without shoes using a beam scale (Avery, Birmingham, U.K.). No subjects had clinically evident edema or ascites.

All subjects underwent venous blood sampling at least 3 wk after surgery or bile duct stenting. The initial 18 patients received full supportive care alone and underwent a further venous blood sample after a median of 28 d. The subsequent 18 patients received 2 cans/d of a nutritional supplement enriched with fish oil providing a total of 2.6 MJ, 32.2 g protein, 99.4 g carbohydrate, 13 g fat, 2.18 g EPA and 0.92 g docosahexaenoic acid (DHA) in a volume of 480 mL (Ross Products Division, Columbus, OH). After a median of 24 d a second venous blood sample was taken.

Assay procedure. Serum and plasma were stored at −70°C until analysis by immunoturbidometry using Tina-Quant assay kits (Boehringer Mannheim, Germany) on a Hitachi 911 analyser (Ealing, UK). The positive APP C-reactive protein, α-1-antitrypsin, α-1-acid glycoprotein, haptoglobin and ceruloplasmin, and the negative APP, albumin, prealbumin and transferrin, were measured at both time-points. The positive APP fibrinogen was measured at baseline only by assessing clotting time in the presence of a high-thrombin concentration on a KC4A Coagulometer (Baxter Healthcare, Thetford, UK). CV of all assays was ≤3%.

Statistics. Data are presented as median and interquartile range. Differences between groups were compared using the Mann-Whitney U test. Changes within groups over time were compared using the Wilcoxon signed rank test. Categorical variables were compared using the Chi-squared test (Statview, Abacus Concepts, Berkeley, CA). A P value of <0.05 is significant.

RESULTS

Subject characteristics. Characteristics of the patient groups and controls are shown in **Table 1**. Patients were well matched for age and disease stage. Cancer patients were slightly older than healthy controls.

Acute phase protein concentrations in cancer patients compared with healthy controls. Serum concentrations of the negative APP, albumin, prealbumin and transferrin were significantly lower in cancer patients than healthy controls (**Fig. 1**A). Concentrations of the positive APP, CRP, fibrinogen, α-1-antitrypsin, α-1-acid glycoprotein, haptoglobin and ceruloplasmin were significantly higher in cancer patients than healthy controls (Fig. 1B).

Effect of feeding nutritional supplement enriched with fish oil on APP concentrations and nutritional status in cancer patients. Patient groups were well matched for baseline serum levels of APP although ceruloplasmin concentration was significantly higher in patients receiving supportive care alone (**Table 2**). In patients receiving the nutritional supplement enriched with fish oil, there were no significant changes from baseline in serum APP levels over the assessment period apart from a rise in the concentration of the negative APP transferrin ($P = 0.031$) (**Fig. 2**). In patients receiving full support-

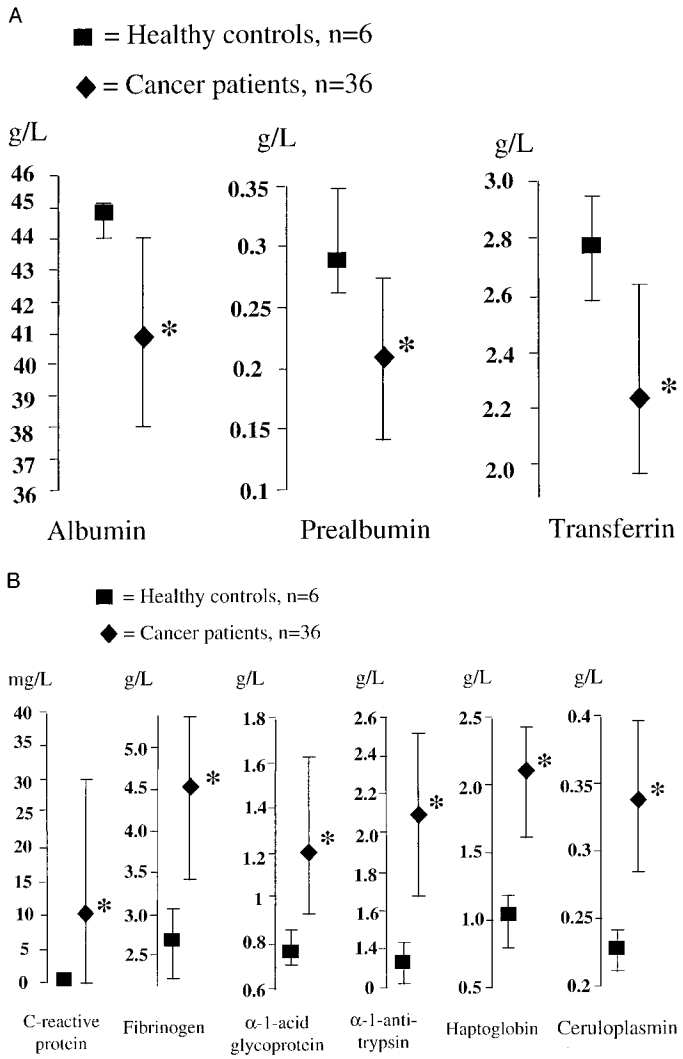

FIGURE 1 Concentrations of negative (*A*) and positive (*B*) acute phase proteins in 36 patients with advanced pancreatic cancer and 6 healthy controls. Graphs show median and interquartile range. Comparison by Mann-Whitney U test. * denotes significantly different from control, $P < 0.04$.

ive care, there was an increase in the concentration of the positive APP CRP ($P = 0.0013$) and a reduction in the concentration of the negative APP albumin, prealbumin and transferrin ($P = 0.012$, 0.0048 and 0.038 respectively). There were significant differences in the changes observed in the serum concentrations of CRP, albumin, prealbumin and transferrin between supplemented and unsupplemented cancer patients over the study period. There was a significant difference in the pattern of weight loss between the two groups with those receiving the supplement gaining a median of 1 kg while those receiving supportive care lost a median of 2.8 kg (**Table 3**).

Overall changes in concentration of acute phase proteins in cancer patients. Total measured positive APP did not change significantly in each group although there was a trend towards an increase in the control group ($P = 0.07$). However, there was a marked difference in the pattern of total production of negative APP between the two patient groups with a significant increase in those receiving the nutritional supplement enriched with fish oil ($P = 0.048$) and a significant decrease in those receiving supportive treatment ($P = 0.016$). Thus, the difference between the groups was highly significant ($P = 0.0012$, **Table 4**).

DISCUSSION

In the present study the concentrations of CRP, fibrinogen, α-1-antitrypsin, α-1-acid glycoprotein, haptoglobin and ceruloplasmin were significantly higher in cancer patients than in healthy controls while albumin, prealbumin and transferrin were significantly lower. This finding reflects the role of these proteins as positive and negative APP respectively (Baumann and Gauldie 1994) and confirms the tendency for patients with advanced cancer to exhibit an APPR as observed previously in pancreatic and other malignancies (Falconer et al. 1994, Staal-van den Brekel et al. 1995, Wayman et al. 1997).

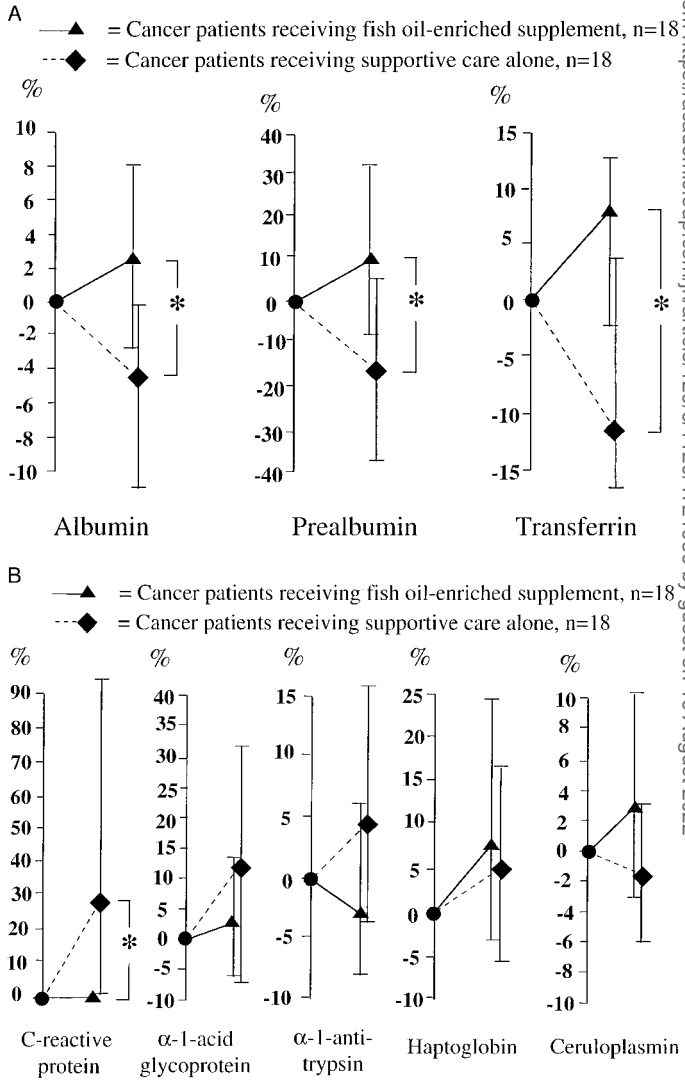

FIGURE 2 Percentage changes in concentrations of negative (*A*) and positive (*B*) acute phase proteins in weight losing patients with advanced pancreatic cancer given either nutritional supplement enriched with fish oil or full supportive care. Graphs show median and interquartile range. Comparison between groups by Mann-Whitney U test. * denotes significant difference between cancer patient groups, $P < 0.04$.

TABLE 2

Baseline serum levels of acute phase proteins (APP) from patients with advanced pancreatic cancer who received a nutritional supplement enriched with fish oil and those who received full supportive care alone

	C-reactive protein [<5][1]	α-1-acid glycoprotein [0.55–1.4]	α-1-antitrypsin [1.1–2.3]	Haptoglobin [0.5–2.0]	Ceruloplasmin [0.15–0.3]	Albumin [36–47]	Prealbumin [0.15–0.4]	Transferrin [2.2–4.0]	Total positive APP	Total negative APP
	mg/L	*g/L*								
Patients receiving supplement	<5[2] (<5–21)	1.12 (0.89–1.39)	2.07 (1.62–2.33)	2.01 (1.45–2.21)	0.30 (0.27–0.35)	41 (38–43)	0.20 (0.14–0.22)	2.17 (1.89–2.61)	5.53 (4.74–6.38)	43.6 (40.2–45.4)
Patients receiving supportive care	11 (<5–30)	1.33 (0.94–2.10)	2.22 (1.76–2.73)	2.26 (1.75–2.63)	0.38[3] (0.32–0.44)	41 (35–44)	0.22 (0.13–0.30)	2.38 (2.01–2.75)	6.28 (5.10–7.40)	43.7 (36.4–46.8)

[1] Normal range.
[2] Values are median (interquartile range).
[3] $P = 0.035$ comparison between patient groups by Mann Whitney U test.

It is possible that the so-called negative APR (albumin, prealbumin and transferrin) might also have been reduced as a result of the relative protein-calorie malnutrition observed in the cancer patients. Indeed, following administration of the fish oil enriched-supplement the weight of patients increased as did transferrin concentration and this may reflect the role of the latter as a fast-turnover hepatic protein sensitive to short-term improvements in nutritional status.

Although hepatocyte albumin secretion may be reduced in vitro by proinflammatory cytokines, (Castell et al. 1990) we have demonstrated recently that in cachectic cancer patients with hypoalbuminaemia and an ongoing APPR, albumin synthesis rates are unaltered. (Fearon et al. 1998) Thus the low-serum albumin concentration observed in the present study is likely to reflect either an increased transcapillary escape rate, an increased degradation rate or a combination of the two. Transcapillary escape has been shown to occur at an elevated rate in weight-losing cancer patients and has been suggested to contribute to the hypoalbuminemia of the APR (Fleck et al. 1985). However, lymphatic return must be similarly increased as there is no relationship between transcapillary escape and albumin concentration (Ballmer et al. 1994) and no change in the intravascular albumin pool with elevated transcapillary escape (Ballmer-Weber et al. 1995). Further study of APP breakdown in cancer is required.

The demand for specific amino acids to manufacture positive APP in patients with an inadequate nutritional intake has been suggested to contribute to ongoing muscle protein breakdown (Reeds et al. 1994) and in a prolonged APPR this may lead to accelerated weight loss and a shortened survival. Although the present study was not a formal randomized trial, cancer patients who received the fish oil–enriched nutritional supplement had no change in the concentration of total positive APP but total negative APP increased compared with patients receiving supportive care alone. This suggests either an attenuation of the APPR, an improvement in nutritional status or, more likely, a combination of the two. The patients receiving supportive care alone had no significant change in total positive APP but sustained a further fall in negative APP. This suggests either progression of the APPR, a further reduction in nutritional status or, again, a combination of the two. It has been suggested, however, that the negative APP are not good indicators of nutritional status in the presence of an APR (Fleck 1989).

The supplement used in this study contained appreciable amounts of the DHA in addition to EPA. DHA is a closely related polyunsaturated fatty acid, also of the (n-3) class, which is metabolised to EPA in vivo (von Schacky & Weber 1985). The relative contribution of these two agents in the present study is not clear. In addition, it is likely that the patients receiving the supplement consumed more calories and protein than those receiving supportive care so it is not possible to discriminate an effect of EPA on the APPR and hence nutritional status from a direct effect of the calories and protein supplied. However, previous studies of conventional oral supplements in cancer patients have demonstrated no effect on either serum albumin concentration or body weight (Evans et al. 1987, Ovesen et al. 1993) suggesting that the effects observed in the present study are at least in part due to the fish oil component of the supplement.

The link between the concentration of various plasma proteins and changes in whole body nitrogen kinetics is complex. Under normal circumstances hepatic protein synthesis is thought to contribute about 15–20% of whole body protein turnover. During an APPR the contribution of hepatic protein synthesis is thought to rise, with the synthesis of individual acute phase reactants increasing markedly (Preston et al. 1998). The measured concentration of a plasma protein is the end result of a variety of processes including synthesis, degradation and distribution between the extravascular and intravascular pools. Thus although synthesis might increase, if

TABLE 3

Baseline weight and change in weight in patients with advanced pancreatic cancer receiving nutritional supplement enriched with fish oil and those receiving full supportive care only

	Initial weight	Change in weight
	kg	*kg/4 week study period*
Cancer patients receiving supplement	55.0[1] (46.5–60.5)	+1.0 (−0.1–+2.0)
Cancer patients receiving supportive care	58.5 (47.8–70.7)	−2.8[2] (−3.7–−1.7)

[1] Values are median (interquartile range).
[2] $P = 0.0001$ comparison between patient groups by Mann Whitney U test.

TABLE 4

Changes in total production of positive and negative acute phase proteins in patients with advanced pancreatic cancer receiving nutritional supplement enriched with fish oil and those receiving full supportive care only over the 4 week study period[1]

	Change in total positive acute phase proteins	Change in total negative acute phase proteins
	g/L	
Cancer patients receiving supplement	−0.02[2] (−0.19–+0.53)	+1.32 (−1.07–+2.95)
Cancer patients receiving supportive care	+0.42 (−0.30–+1.24)	−2.44[3] (−5.72–+0.28)

[1] Measured positive acute phase proteins were C-reactive protein, α-1-antitrypsin,α-1-acid glycoprotein, haptoglobin and ceruloplasmin. Measured negative acute phase proteins were albumin, prealbumin and transferrin.
[2] Values are median (interquartile range).
[3] $P = 0.0012$ comparison between patient groups by Mann Whitney U test.

degradation also increases the net effect may be no change in the plasma concentration but a significant alteration in overall protein turnover. If the latter process is not 100% efficient, this would result in net protein loss from the body and accelerated wasting. We have previously demonstated that in fasting cancer patients with an ongoing APPR fibrinogen synthesis is increased by ~200% while the plasma concentration is increased by ~50% (Preston et al. 1998). However, while the rate of albumin synthesis is unchanged plasma concentrations may be decreased by ~25% (Fearon et al. 1998). Thus interpretation of the changes in APP concentrations in the present study requires kinetic studies in order to determine their true relation to nutritional status in general and nitrogen economy in particular. Unfortunately, examination of the synthesis and more so, degradation of many APP, is difficult due to their relatively low-circulating concentrations.

Several explanations exist for the mechanism of the apparent stabilization of the APPR in patients receiving the fish oil–enriched supplement observed in the present study. In vitro, the APPR is largely regulated by IL-6 (Castell et al. 1990). We have previously shown that patients with advanced pancreatic cancer exhibiting an APPR have elevated production of IL-6 by isolated peripheral blood mononuclear cells (Falconer et al. 1994) and that the administration of a pure preparation of EPA will reduce this production of IL-6 to control levels (Wigmore et al. 1997a). In addition, the production of proinflammatory cytokines and APP is controlled to some extent by the transcription factor NF-κB (Beauparlant and Hiscott 1996). Polyunsaturated fatty acids have been shown to activate NF-κB but initial work suggests that EPA has little effect on this pathway in vitro (Camandola et al. 1996). The administration of polyunsaturated fatty acids to hepatocytes in culture has suggested that EPA may have direct effects on the modulation of APP production (Wigmore et al. 1997b). Additional elucidation of the mechanism of action of the fish oil–enriched supplement used in the present study and the relative contributions of its components requires further study.

In summary the present study suggests that fish oil, rich in (n-3) fatty acids, in combination with a nutritional supplement, is able to prevent progression of the APPR and cachexia in weight losing patients with advanced cancer. Possible benefits of these findings in terms of patient quality of life and survival deserve further study in a formal randomized controlled trial.

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