

## Systematic Review

### ***n*-3 Fatty acids, cancer and cachexia: a systematic review of the literature**

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Use of *n*-3 fatty acids (FA) has been reported to be beneficial for cancer patients. We performed a systematic review of the literature in order to issue recommendations on the clinical use of *n*-3 FA in the cancer setting. A systematic search was performed in MEDLINE, EMBASE, Cochrane and Healthstar databases. We selected clinical trials or prospective observational studies including patients with cancer and life expectancy >2 months, in which enteral supplements with *n*-3 FA were administered. Parameters evaluated individually were clinical (nutritional status, tolerance, survival and hospital stays), biochemical (inflammatory mediators), and functional (functional status, appetite and quality of life (QoL)). Seventeen studies met the inclusion criteria; eight were of high quality. The panel of experts established the following evidence: (1) oral supplements with *n*-3 FA benefit patients with advanced cancer and weight loss, and are indicated in tumours of the upper digestive tract and pancreas; (2) the advantages observed were: increased weight and appetite, improved QoL, and reduced post-surgical morbidity; (3) there is no defined pattern for combining different *n*-3 FA, and it is recommended to administer >1.5 g/day; and (4) better tolerance is obtained administering low-fat formulas for a period of at least 8 weeks. All the evidences were grade B but for 'length of treatment' and 'advantage of survival' it was grade C. Our findings suggest that administration of *n*-3 FA (EPA and DHA) in doses of at least 1.5 g/day for a prolonged period of time to patients with advanced cancer is associated with an improvement in clinical, biological and QoL parameters.

#### ***n*-3 fatty acids: EPA: DHA: Cancer: Cachexia: Nutrition**

*n*-3 and *n*-6 PUFA are named according to the position of the first double bond from the methyl terminus of the hydrocarbon chain of the molecule. Most of the *n*-6 and *n*-3 PUFA are metabolised from precursors, linoleic acid (18:2*n*-6) and  $\alpha$ -linolenic acid (18:3*n*-3), respectively, by a series of elongation and desaturation reactions to yield longer, more unsaturated fatty acids (FA) (Karmali, 1996).

*n*-3 and *n*-6 PUFA have a number of vital functions in the human body as structural phospholipids of the cell membrane; they modulate membrane fluidity, cellular signalling and cellular interaction (Kelley, 2001; Vancassel *et al.* 2001).

While *n*-6 FA have potent inflammatory effects, *n*-3 FA have lesser pro-inflammatory effects, and these two classes of FA compete in the production of inflammatory lipid

mediators. These potent immunoregulatory metabolites are synthesised from 20-C PUFA precursors. EPA or arachidonic acid are mobilised from the cell membrane by the action of phospholipase enzymes, especially phospholipase A2 and phospholipase C, and subsequently metabolised by cyclooxygenase or lipoxygenase enzymes into PG, thromboxanes and leukotrienes. EPA gives rise to 3-series PG and thromboxanes and 5-series leukotrienes, the difference being the presence of an additional double bond in the structure. Because cell membrane phospholipids normally contain much higher levels of arachidonic acid than of the other 20-C PUFA, arachidonic acid is the most common eicosanoid precursor and gives rise to 2-series PG and thromboxanes and 4-series leukotrienes.

**Abbreviations:** FA, fatty acids; QoL, quality of life.

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*n*-3 FA (e.g. EPA and DHA) reduce production of inflammatory cytokines associated with several chronic diseases, anorexia associated with these diseases and anorexia associated with immunotherapy with these cytokines (Meydani, 1996).

Many factors influence tumour induction and cancer growth, including a range of cytokines and growth factors, and genotoxic and oxidative stress. During cancer progression, cell turnover, differentiation and apoptosis are impaired. *n*-3 PUFA have emerged as anti-carcinogenic nutrients of potential benefit in cancer, through regulation of either enzyme expression and/or activity and end-product concentrations, or by modulating the levels of available precursors for biosynthetic pathways. They work through several actions to protect against the initiation and early stages of cancer, including decreasing tumour cell proliferation, enhancing tumour cell apoptosis, promoting cell differentiation, and limiting angiogenesis (Roynette *et al.* 2004).

During the past 20 years, several dozen studies have investigated the effects of *n*-3 PUFA on human immune and inflammatory responses. Most of these studies involved supplementing diets with marine oils containing EPA and DHA or purified EPA and DHA. These promising results prompted us to conduct this systematic review, which was first discussed by a panel of experts and finally presented in this document.

## Materials and methods

The systemised review has been designed according to the Quorum statement (Moher *et al.* 1999). We located and subsequently analysed the scientific literature available from 1996 to 2006 in several of the most widely used databases, including MEDLINE, EMBASE, The Cochrane Library databases on clinical trials and the online version of the Healthstar database. The search terms used for the review were: fish oil, fatty acid, epa, eicosapentaenoic, docosahexaenoic, omega 3, tumour, neoplasm, cancer, carcinoma, appetite, cachexia, economics, cost analysis, cost benefit and quality of life (QoL). Bibliographies were checked, and experts in the field were contacted for additional studies. The realisation of a quantitative analysis of the selected papers was not considered, due to the small sample of the studied populations and also because the heterogeneity of the papers would not assure the reliability of the results. The inclusion criteria for studies selected for analysis were those including patients of both sexes aged > 18 years with malignant neoplasms associated with cachectic syndrome, a life expectancy > 2 months, and not undergoing chemotherapy or radiotherapy at the time of the study. Studies on patients treated with surgery for potentially cachectising gastrointestinal malignancies were also included.

Studies on patients with potentially cachectising concomitant diseases such as renal or heart failure and autoimmune diseases, or patients with potentially hormone-sensitive or emetogenic brain, breast, ovarian, prostate or endometrial cancer that would prevent proper oral intake were excluded.

The selected studies were analysed by two independent reviewers who coded the results separately and resolved any discrepancies by discussion and consensus between them. When there was no consensus, a third reviewer resolved the differences found. The results were presented to a panel of experts selected from among the different medical specialties related to the subject of the study (oncology, endocrinology,

general surgery and intensive medicine), all of whom were opinion leaders in the nutritional implications in their field.

Studies existing in the medical literature with a higher level of scientific evidence were selected, including meta-analyses of clinical trials, clinical trials and prospective observational studies with large samples (on those issues where clinical trials were not located), economic evaluations of health technologies and qualitative studies. The study design aspects assessed to consider a study of high scientific quality were: randomised assignment of control and experimental groups, existence of a concurrent control group, prospective design, use of blinding, and sample size sufficient to detect significant differences. Studies conducted in animals or in languages other than English, French or Spanish were not considered.

The studies collected could analyse biochemical, clinical and functional parameters following nutritional support with supplements enriched with *n*-3 FA EPA and DHA over a variable period up to 3 months. The following clinical outcomes were noted: nutritional status, tolerance and gastrointestinal complications, incidence of post-surgical infection, length of hospital stay and survival. The functional parameters collected were: appetite, disease-specific and overall QoL (Karnofsky scale and ECOG performance status scale). Laboratory parameters analysed included plasma FA composition, pro-inflammatory response mediators: TNF, IL-1, IL-6, PG, and C-reactive protein as a marker of inflammatory response.

Two independent reviewers selected and analysed the information collected. Studies were classified according to the level of evidence based on the table prepared by the Agència d'Avaluació de Tecnologia Mèdica (Jovell & Navarro Rubio, 1995) (Table 1). Based on the analysis and evaluation of the evidence collected, recommendations were subsequently formulated on the suitability of the conditions for adoption of a health technology or intervention according to the recommendation grades established by the Canadian Task Force (<http://www.ctfphc.org>) (Table 2). Finally, the quality of the clinical trials collected was assessed using the scale proposed by Jadad *et al.* (1996) which is illustrated in Fig. 1.

## Results and evidence recommendations

Fifty clinical trials and prospective studies were reviewed and analysed. Of these, only seventeen met the selection criteria. The studies that were selected for evaluation are summarised in Table 3. Relevant aspects regarding the design, results and conclusions of each study are shown in the table. In the level of evidence column, the quality grade assigned to each of the clinical trials is indicated. The final assessment and evidence grade were agreed by consensus by the panel of experts. A summary of the quality of the studies by the different parameters analysed is shown in Table 4.

*Is the provision of supplements containing n-3 fatty acids beneficial in cancer patients?*

Yes, in patients with advanced cancer and weight loss.

Recommendation grade: B

*In which type of tumours?*

*Pancreas and upper digestive tract cancer.* There are currently no studies on other types of neoplasms, although a

**Table 1.** Level of evidence for study classification according to the Agència d'Avaluació de Tecnologia Mèdica (Jovell & Navarro Rubio, 1995)

Level	Type of design	Study characteristics
I	Meta-analysis of randomised controlled trials	Non heterogeneity Different techniques of analysis Meta-regression Mega analysis Quality of studies
II	Randomised controlled trials with large samples sizes	Evaluation of statistical power Multicentre Quality of study
III	Randomised controlled trials with small sample sizes	Evaluation of statistical power Quality of study
IV	Non-randomised controlled prospective trials	Concurrent controls Multicentre Quality of study
V	Non-randomised controlled prospective trials	Historic controls Quality of study
VI	Cohort studies	Multicentre Paired design Quality of study
VII	Case-controlled studies	Multicentre Quality of study
VIII	Non-controlled clinical series	Descriptive studies Expert committees
IX	Anecdotal or single cases	Multicentre

recent study (Jatoi *et al.* 2004) showed good results in terms of weight maintenance or gain in various solid tumours.

Recommendation grade: B

*Is there an appropriate fatty acid pattern?*

The higher quality studies (Kenler *et al.* 1996; Fearon *et al.* 2003; Burns *et al.* 2004; Jatoi *et al.* 2004) used combinations of EPA and DHA in a 2 : 1 ratio. Some studies (Wigmore *et al.* 1996; Gogos *et al.* 1998; Zuijdggest-Van Leeuwen *et al.* 2000) with positive results used EPA only.

Recommendation grade: B

*What is the recommended dose?*

Available data recommend the administration of 1.5 to 2 g EPA/day. Although Fearon *et al.* (2003) and Wigmore *et al.* (1996) found no advantages in exceeding 2 g/day, Burns administered much higher doses with good results (4.7 g EPA/day).

Recommendation grade: B

*What is their tolerance and safety?*

The incidence of adverse effects at the recommended doses is low. Although there is no direct recommendation, better tolerance has been reported when EPA was administered as part of a low-fat nutritional formula (Fearon *et al.* 2003) than as concentrated capsules (Burns *et al.* 2004, Bruera *et al.* 2003).

Recommendation grade: B

**Table 2.** Recommendation grades for specific clinical preventive actions according to the Canadian Task Force (CTF)

<b>A</b>	The CTF concludes that there is <i>good</i> evidence to recommend the clinical preventive action.
<b>B</b>	The CTF concludes that there is <i>fair</i> evidence to recommend the clinical preventive action.
<b>C</b>	The CTF concludes that the existing evidence is <i>conflicting</i> and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making.
<b>D</b>	The CTF concludes that there is <i>fair</i> evidence to recommend against the clinical preventive action.
<b>E</b>	The CTF concludes that there is <i>good</i> evidence to recommend against the clinical preventive action.
<b>I</b>	The CTF concludes that there is <i>insufficient</i> evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

*How long should they be given?*

One higher quality study in patients with advanced pancreatic cancer (Fearon *et al.* 2003) recommends at least 8 weeks. Positive clinical effects have been observed in post-surgical patients from 1 week of treatment. Some biological markers have shown improvement after 1 week of nutritional treatment.

Given the low incidence of adverse effects at the recommended doses, treatment can be maintained for as long as there are objective benefits.

Recommendation grade: C

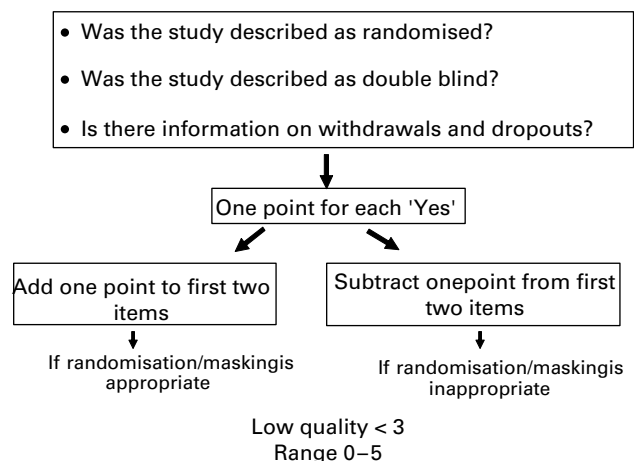
*Are there markers of efficacy and effectiveness?*

It is recommended to assess efficacy using anthropometric measures (weight, BMI), bioimpedance (lean mass), functional parameters and QoL scales.

Recommendation grade: B

*Are there any advantages in terms of survival?*

The study by Gogos *et al.* (1998) showed statistically significant advantages in survival ( $P < 0.025$ ). These differences increased ( $P < 0.001$ ) when well-nourished patients fed supplement were compared to malnourished patients fed placebo. The Fearon *et al.* (2003) study did not find differences in survival as well as the study by Jatoi *et al.* (2004) when



**Fig. 1.** Grading of clinical trial quality (after Jadad *et al.* 1996).

**Table 3.** Summary of the selected studies

Author	Design	Population	Intervention	Results	Conclusions	Level of evidence	CT quality*
Barber <i>et al.</i> 1999a	Prospective Non-blinded Non-controlled Non-randomised	20 patients. Non-resectable pancreatic cancer.	2.2 g EPA + 0.96 g DHA 3 and 7 weeks	Significant weight gain in 3 and 7 weeks of 1 and 2 kg, respectively, at the expense of lean body mass. Significant improvement in Karnofsky functional status and appetite. Decrease in resting energy expenditure. No changes in C-reactive protein. Significant improvement in Karnofsky functional status and appetite, mean survival of 170 d.	<i>n</i> -3 fatty acid energy supplements produce improvement in functional status and appetite and weight gain, reversing cachexia in patients with pancreatic cancer.	V	NA
Barber <i>et al.</i> 1999b	Clinical trial Controlled Non-randomised	36 patients. Advanced pancreatic cancer + 6 healthy subjects.	E group: 2 g EPA + 1 g DHA/d 3 weeks C group: no supplements	No changes in ceruloplasmin, C-reactive protein and other acute phase proteins in E group. Increase in transferrin measured at 4 weeks. Significant weight gain in E group.	Acute phase reactants tend to increase in C group and to stabilise in patients administered <i>n</i> -3 supplements. These supplements prevent acute-phase protein response and wasting in patients with advanced pancreatic cancer.	IV	1
Barber <i>et al.</i> 2000	Prospective Non-blinded Non-randomised	16 patients with pancreatic cancer. 6 healthy controls.	Diet with 2.2 g EPA + 0.96 g DHA 3 weeks	Significant weight gain of 1 kg at the expense of lean body mass. Increase in energy expenditure of 9.6%. Elevated postprandial serum insulin concentrations after supplementation. No significant changes in cortisol concentrations.	EPA-enriched nutritional supplements reduce resting energy expenditure in cancer patients.	V	NA
Barber <i>et al.</i> 2001a	Prospective Non-blinded Non-randomised Non-controlled	20 patients with non-resectable pancreatic cancer.	600 Kcal + 2 g EPA/d 3 weeks	Significant fall in IL-6, rise in serum insulin, and fall in proteolysis inducing factor. Significant weight gain of 1 kg.	<i>n</i> -3 fatty acids modulate mediators of catabolism in cachexia and induce weight gain.	V	NA
Barber <i>et al.</i> 2001b	Prospective Non-blinded Non-randomised	5 patients with advanced pancreatic cancer.	Starting dose 18 g EPA diester emulsion/day Doses administered 9 to 27 g/d for 1 month	Dose limited by a sensation of fullness, cramping abdominal pain, steatorrhea and nausea. Plasma EPA content of 1% at baseline to 20% at 8 weeks.	Doses of 18 g EPA per day are well tolerated and side effects are easily controlled.	V	NA
Bruera <i>et al.</i> 2003	Clinical trial Controlled Blinded Randomised	60 patients	18 capsules/day: E group: 180 mg EPA + 120 mg DHA per capsule + Vitamin E (30 pts) C group: 1000 mg olive oil 14 days	No differences between two groups in: appetite, weight, caloric intake, Karnofsky functional status, well-being, nausea and vomiting.	Fish oil does not significantly improve appetite, nausea, well-being, caloric intake, and nutritional status compared to olive oil.	III	3
Burns <i>et al.</i> 1999	Clinical trial Non-blinded Non-randomised	25 patients. Incurable cancers with life expectancy > 2 months	1 month of escalating doses up to a maximum tolerated dose of 0.3 g/kg per d (fish oil capsules, EPA + DHA)	Gastrointestinal toxicity: steatorrhea, diarrhoea, abdominal cramping, nausea and vomiting. Weight changes were controlled at two months with no further weight loss. Mean survival: 134 days	Patients with advanced cancer tolerate large doses with minor side effects. Administration of <i>n</i> -3 supplements is reasonable given the expected life span and may reverse cachexia.	IV	1

Table 3. Continued

Author	Design	Population	Intervention	Results	Conclusions	Level of evidence	CT quality*
Burns P <i>et al.</i> 2004	Clinical trial Non-controlled Non-blinded Non-randomised	43 patients with solid tumours.	Capsules 7.7 g EPA +2.8 g DHA 1.2 months	Weight stabilisation: 66%. Weight gain: 17%. Survival: 3.7 months. Best QoL scores in patients with weight gain.	The majority of patients maintained weight and only 17% gained weight with doses twice the usual dose.	III	1
Fearon <i>et al.</i> 2003	Clinical trial Multicentre Controlled Randomised Blinded	Control (C) group: <i>n</i> 105. Experimental (E) group: <i>n</i> 95 Total <i>n</i> 200 Pancreatic cancer.	E group: 2 cans with 1.1 g EPA/can + antioxidants per day + DHA C group: No EPA no DHA (Mean1 intake of 1.4 cans/day) 8 weeks	Weight stabilisation in both groups. When the dose of EPA is greater than 1.5 g/day, there is a net gain of weight, lean tissue, and improved QoL.	The effective dose of EPA is greater than 1.5 g/day. Plasma EPA levels were identified as a marker of treatment efficacy.	II	5
Gogos <i>et al.</i> 1998	Clinical trial Controlled Randomised Non-blinded	WN Group: good nutritional status ( <i>n</i> 30) MN Group: poor nutritional status ( <i>n</i> 30) Total <i>n</i> 64	Group A ( <i>n</i> 30): 18 g/day fish oil (capsules) (170 mg EPA + 115 mg DHA) Group B ( <i>n</i> 30): sugar Median of 40 days to 10 months	A group: Increase in T helper cells. Increase in TNF in A and MN groups. No differences in IL1, IL6. No differences in weight and plasma albumin. Improved Karnofsky functional status in A and WM groups. Greater survival in WN and MN groups. No differences in hospital stay or incidence of infections.	<i>n</i> -3 Fatty acid supplements have a significant immunomodulatory effect and prolong survival in patients with malignancies and poor physical status.	III	2
Jatoi <i>et al.</i> 2004	Clinical trial Controlled. Blinded Randomised	421 patients with solid tumours.	2 g EPA + 1 g DHA v. 600 mg Megestrol v. both	Weight gain > 10%: 6 (EPA), 18 (M) and 11% (both) Appetite: 64 (EPA), 68 (M) and 66% (both) No differences in survival or QoL	Megestrol showed better efficacy for weight gain, without differences in appetite, survival or QoL.	II	4
Kenler <i>et al.</i> 1996	Clinical trial Controlled Blinded Randomised	50 patients. Surgically operated upper gastrointestinal malignancies	E group: 3.27 g EPA + 1.48 g DHA/day 7 days Plus TPN	No differences in laboratory biochemical parameters. Significant 50% reduction in gastrointestinal complications: distension, diarrhoea, and nausea in E group. Trend toward lower incidence of infections and suture dehiscence in E group. Significant decrease in need for TPN in E group. Improvement in liver and renal function.	Results suggest that early use of <i>n</i> -3 supplements in the post-operative period reduces the number of infections and gastrointestinal complications and improves liver and renal function due to its modulatory effect on prostaglandins.	III	2
Moses <i>et al.</i> 2004	Clinical trial Controlled Blinded Randomised	24 patients. 12 C and 7 E. Pancreatic cancer.	3.2 g <i>n</i> -3 (EPA) 8 weeks	Significant increase in total resting energy expenditure and physical activity level.	In cachectic patients with pancreatic cancer, administration of supplements enriched with EPA for 8 weeks is associated with an increase in total energy expenditure and physical activity level.	III	5

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Table 3. *Continued*

Author	Design	Population	Intervention	Results	Conclusions	Level of evidence	CT quality*
Swails <i>et al.</i> 1997	Clinical trial Controlled Blinded Randomised	20 patients. Surgically operated upper gastrointestinal malignancies	E group: 3.27 g EPA + 1.48 g DHA /day 7 days	No differences in laboratory biochemical parameters or nitrogen balance. No differences in gastrointestinal tolerance. Trend toward fewer infections and suture dehiscences in E group. Significant reduction in PGE2 and 6-keto PGF1 production from PBMC in E group.	Early enteral feeding with EPA and DHA in surgical patients is associated with a reduction in eicosanoid production from PBMC.	III	2
Wigmore <i>et al.</i> 1996b	Clinical trial Randomised Controlled	18 patients with advanced stage pancreatic cancer	12 g capsules of fish oil (18% EPA + 12% DHA)/d 3 months	Tolerance of 12 g fish oil (2 g/d EPA). Steatorrhea 25%. Mean weight gain: 0.3 kg/ month $P < 0.002$ . Significant decrease in C-reactive protein. Stabilisation of resting energy expenditure by indirect calorimetry	<i>n</i> -3 may have anti cachectic effects in cancer patients.	IV	1
Wigmore <i>et al.</i> 2000	Prospective Non-blinded Non-randomised Non-controlled	26 patients. Advanced pancreatic cancer.	1 g/d EPA (capsules) up to 6 g/d in 4 weeks and then 6 g/d for 12 weeks	Weight gain of 0.5 kg at 1 month, which remained stable at 12 weeks. Survival of 203 days.	EPA is safe and well tolerated, and stabilizes weight in patients with tumour cachexia.	V	NA
Zuijdgeest-Van <i>et al.</i> 2000	Clinical trial Double Blind Randomised Controlled	16 healthy controls. 17 cancer patients. <i>n</i> 33	8 healthy controls and 9 patients: 6 g EPA 8 healthy controls and 8 patients 6 g oleic acid (capsules) 7 days	Lipolysis or increase in palmitic acid: NS. Oxidised palmitate: NS. EPA significantly reduced triacylglycerol and free fatty acids ( $P < 0.005$ ) in healthy subjects.	EPA does not inhibit lipolysis or lipid oxidation compared to oleic acid.	III	3

'Level of evidence' refers to study characteristics according to type of design, as described in Table; CT, clinical trial; E group, experimental group; C group, control group; NA, not applicable; M, megestrol acetate; WN, well nourished; MN, malnourished; PBMC, peripheral blood mononuclear cells.

\*Quality grade agreed by expert panel.

Table 4. Results by parameters analysed

Parameter	Higher quality clinical trials (level > III)	Lower quality clinical trials and observational studies (level < III)*
Weight and/or lean mass gain	Gogos <i>et al.</i> 1998; Fearon <i>et al.</i> 2003; Burns <i>et al.</i> 2004; Jatoi <i>et al.</i> 2004	Wigmore <i>et al.</i> 1996; Burns <i>et al.</i> 1999; Barber <i>et al.</i> 1999a; Barber <i>et al.</i> 1999b; Wigmore <i>et al.</i> 2000; Barber <i>et al.</i> 2000; Barber & Fearon, 2001b; Wigmore <i>et al.</i> 1996; Barber <i>et al.</i> 1999a; Barber & Fearon, 2001b
Energy expenditure/oxidation	Zuijgeest <i>et al.</i> 2000; Bruera <i>et al.</i> 2003; Moses <i>et al.</i> 2004	
Increased survival	Gogos <i>et al.</i> 1998	Wigmore <i>et al.</i> 1996; Burns <i>et al.</i> 1999; Barber <i>et al.</i> 2001a
Tolerance of formula	Gogos <i>et al.</i> 1998	Gogos <i>et al.</i> 1998
Post-surgical morbidity	Kenler <i>et al.</i> 1996; Gogos <i>et al.</i> 1998	Barber <i>et al.</i> 1999a
Appetite	Bruera <i>et al.</i> 2003	Barber <i>et al.</i> 1999a
Quality of life, functional status	Gogos <i>et al.</i> 1998; Bruera <i>et al.</i> 2003; Fearon <i>et al.</i> 2004; Moses <i>et al.</i> 2003; Swails <i>et al.</i> 1997	Wigmore <i>et al.</i> 1996b; Gogos <i>et al.</i> 1998; Barber <i>et al.</i> 1999a; Barber <i>et al.</i> 1999b; Barber <i>et al.</i> 2000
Inflammatory mediators		

\*As described in Table 1.

compared with megestrol acetate, anyhow it was not placebo controlled.

Recommendation grade: C

## Discussion

The anti-inflammatory effects of *n*-3 PUFA and their beneficial effects for cardiovascular health have prompted a number of studies on the management of autoimmune and inflammatory diseases. Fish-oil supplementation has reduced the symptoms of several diseases such as Ig-A nephropathy, asthma, and Crohn's inflammatory-bowel disease. Other conditions that were improved with *n*-3 FA supplementation include: arthritis, ulcerative colitis, lupus, psoriasis, cystic fibrosis, re-stenosis after angioplasty, and renal functions after liver or kidney transplantation. It also decreased circulating levels of IL-1, IL-2, IL-4, IL-6, TNF, and  $\gamma$ -interferon in patients with advanced colorectal cancer, improved survival of patients with cancers of different organs, and reduced weight loss in patients with pancreatic cancer (Wigmore *et al.* 1996). The intake of fish oils in those studies ranged from 4 to 20 g/d for 6 weeks to 60 months (Kelley, 2001; Roynette *et al.* 2004).

According to our systematic review, in neoplastic diseases the provision of diets supplemented with *n*-3 FA showed measurable benefits in the different biochemical, clinical and functional parameters considered. The majority of the studies support with varying grades of recommendations supplementation with diets rich in *n*-3 FA in this type of patients. Elia *et al.* (2006) reached similar conclusions in their systematic review for enterally fed patients as well as those taking oral supplements with a decrease in the complications, especially the infectious ones, as well as a decrease in hospital stays and an improvement in the inflammatory markers.

The most appropriate proportion of *n*-6 and *n*-3 FA is a controversial subject. Because of their respective anti-inflammatory and pro-inflammatory natures, the *n*-6:*n*-3 FA ratio should be kept as low as possible (Xia *et al.* 2005) One of the possible ways to achieve this is to keep the proportion of lipids low, which additionally has the positive effect of achieving a reduced satiating effect. In the studies considered, the *n*-6:*n*-3 FA ratio was approximately 1:3.

Dose of EPA is an issue of great concern. Although some of the best trials have not achieved a dose greater than 1.5 g/d other studies have found increased benefit with higher doses (between 1.5 and 4 g/d). This probably means that under 1.5 g/d there is hardly any effect and that superior doses may obtain improved results.

The negative results obtained in the study by Bruera *et al.* (2003) should be noted, and, in our opinion, were due to the use of a patient group with tumours of very diverse origin (we found clear efficacy in cancer of the pancreas and upper digestive tract) who were treated nutritionally for a short period of 2 weeks, although they later received unmasked treatment for a longer period (treatment time was 7 weeks in the study by Barber *et al.* (1999a) and 8 weeks in the study by Fearon *et al.* (2003).

Jatoi *et al.* (2004) showed increased weight and appetite in their study of patients treated with EPA. Both patients with gastrointestinal and lung tumours showed lower percentages of weight gain and appetite than those previously reported by other authors and lower than those observed in their study of

megestrol, another drug with proven efficacy as an anti-anorexic agent. However, no differences were found versus megestrol with respect to appetite, QoL or overall survival.

Finally, it should be noted that most of the studies analysed reported better tolerance when EPA was administered as part of a low-fat nutritional formula instead of in the form of concentrated capsules. On the other hand the role of DHA separated from EPA has not been clearly ascertained in human subjects as most trials deal with both products in combination.

## Conclusions

In cancer patients, supplementation with FA (EPA and/or DHA) in the diet or in the form of concentrated capsules seems to be associated with an improvement in various clinical, biochemical and QoL parameters. Regarding duration of supplementation evidence is conflicting but data suggest that good results can be obtained with prolonged nutrition (8 weeks).

It is recommended that prospective studies be carried out to relate the efficacy of nutritional support with EPA in terms of both clinical parameters (body mass, survival and QoL) and biochemical parameters (plasma levels of EPA, C-reactive protein and PG).

We can conclude that, although prognosis has traditionally been defined in terms of morbidity and mortality, we should currently incorporate multidimensional concepts that include measures of functional status, QoL, patient satisfaction and economic evaluation. This is extremely important in situations where the patients, as in this systematic review, are cancer patients with associated cachexia, since application of any support in such patients must be shown to be effective (Resolution ResAP (2003)3).

We were unable to evaluate economic outcomes or cost-effectiveness/utility in this systematic review due to the lack of this information in the studies used (Voss & Gallagher-Allred, 1996).

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