**Abstract**

**Introduction**

Existing guidelines on nutrition support in patients with cancer cachexia state limited evidence for the beneficial effects of n-3 polyunsaturated fatty acids (PUFAs) on clinical outcome. In order to report on the latest evidence for n-3 PUFAs in cancer cachexia, we conducted a systematic literature review of randomized controlled trials (RCTs), comparing the effects on clinical outcome parameters of oral or enteral supplementation of n-3 PUFAs in cancer patients receiving chemotherapy, radiotherapy, surgery or palliative care.

**Materials and methods**

In PubMed, EMBASE and the Cochrane Library, search terms on cancer, n-3 PUFAs and clinical outcome parameters (nutritional status, morbidity, mortality and quality of life) were entered on 1 April 2013, using limits for adults, humans and English language. The quality and evidence of the retrieved publications were appraised by an expert team of Australian and Dutch dieticians and nutritionists, using the ADA grading system. Fifteen RCTs were retrieved.

**Results**

Nine RCTs were of positive quality, five of neutral quality and one of negative quality and were performed in patients with various types of cancer. Fair evidence shows that supplementation of n-3 PUFAs appears to be safe and may improve the quality of life and physical activity in patients with cancer. However, supplementation of n-3 PUFAs does not improve energy or protein intake, appetite or survival and does not reduce postoperative complications. The evidence for the effect on body weight, fat-free mass and performance status remains inconclusive.

**Conclusion**

Supplementation of n-3 PUFAs may have some positive effects in patients with cancer.

**Introduction**

Cancer cachexia, a complex metabolic syndrome associated with underlying illness, characterized by an increased inflammatory status and loss of muscle mass with or without loss of fat mass, is highly prevalent among patients with cancer. This syndrome is a result of complex alterations in carbohydrate, lipid and protein metabolism, caused by inflammatory mediators such as cytokines and tumour-derived catabolic drivers. Proteolysis-inducing factor (PIF) is produced by the tumour and induces protein catabolism. As a result of the acute phase response, the liver shows an increased protein turnover for the production of inflammatory mediators, using muscle mass to release amino acids.

Changes in lipid metabolism in cancer include a reduction of lipogenesis, with unchanged whole-body lipolysis and mobilization of fatty acids from fat tissue. Alterations in glucose metabolism are reflected by glucose intolerance and insulin resistance.

Thus far, conventional nutritional support has been limited in its ability to stabilize body weight and maintain fat-free mass in patients with cachexia. Pharmaceutical interventions sometimes improved appetite, body weight and quality of life, but weight gain mostly consisted of fat mass.

n-3 Polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA), seem to be promising agents to treat cancer cachexia. A dose of around 2 g of EPA per day (alone or combined with docosahexaenoic acid, DHA) appears to decrease the production of proinflammatory cytokines and PIF and is associated with stabilization of body weight and probably fat-free mass. This has been shown in animal studies and in nonrandomized human trials in pancreatic cancer patients. However, randomized controlled trials (RCTs) show contradictory results. This may be due to issues related to study limitations, such as the disease severity, confounding factors and nonadherence with n-3 PUFA supplements. Also, study designs and outcome parameters differ in terms of supplementation dosage.

**Competing interests:** none declared. Conflict of interests: none declared.

All authors contributed to the design, conduct, interpretation, preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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comparison with control or other agents and outcome parameters. Body weight is the most frequently used primary outcome measure, but may be biased by fluid retention. Another important issue is the heterogeneity in the assessment of cachexia and weight loss in clinical studies.

From clinical and research perspectives, there is a need for an updated literature overview on the effectiveness of n-3 PUFAs in patients with cancer. In the past, several reviews and nutrition guidelines have addressed the issue of the prescription of n-3 PUFAs in patients with cancer cachexia. Overall, these guidelines conclude that there are some indications for the beneficial effects of n-3 PUFAs on body weight and physical function in cancer patients, but no effects on survival. The available reviews only included studies that were published before 2000. We previously published a systematic review and included studies published until April 2011. Since then, there have been several new studies and reviews published in this field.

Therefore, the aim of this systematic review is to report on the latest evidence for the effects of n-3 PUFAs on clinical outcome parameters in patients with cancer and provide recommendations for use in clinical practice.

Materials and methods
Patient characteristics
This systematic review of RCTs involved adult (≥ 18 years of age) patients with cancer.

Literature search
A literature search was performed on 1 April 2013, using three databases: PubMed (start date 1948), EMBASE (start date 1986) and the Cochrane Library (start date 2005). Medical subject headings (MeSH or Entree) and free text words for n-3 PUFAs, EPA, cancer and clinical outcome parameters (body weight, fat-free mass, morbidity, mortality, length of stay and quality of life) were used to select relevant publications (supplementary Table 1). Any oral or enteral administration of n-3 PUFAs was included: (fish oil) capsules, oral nutritional supplements (ONSs) or tube feeding containing n-3 PUFAs. Studies investigating multiple immune-enhancing compounds (e.g. arginine, glutamine, nucleotides and n-3 FAs) or studies with concurrent use of appetite stimulants were excluded. The literature search was limited to RCTs in adult human subjects, which were available in English. Nonplacebo-controlled studies and single-arm studies were excluded. In case a study was reported in more than one publication, the earliest publication reporting at least one relevant outcome variable was included. Two members of the expert committee (BvdM and MvB) assessed the eligibility of publications on n-3 PUFAs in cancer patients by reviewing the title and abstract and included eligible studies. Moreover, reference lists of included articles were reviewed to identify eligible studies, which were not retrieved by the literature search.

Study quality and strength of the evidence
BvdM composed an expert team of Australian and Dutch dieticians and nutritionists during an International Cancer Technology Transfer fellowship from the UICC in Brisbane, Australia. The aim of the expert team was to appraise the included studies and to compose evidence statements and recommendations to be used for clinical practice.

Two independent members of the expert team appraised the quality of individual studies using the Quality Criteria Checklist of the online accessible Evidence Analysis Library of the American Dietetic Association (ADA). The checklist includes four relevance questions that address applicability to dietetic practice and 10 validity questions that address scientific soundness, most importantly on potential selection bias, randomization and blinding procedures and the validity and reliability of outcome parameters. Study quality was rated as positive (+), neutral (∅) or negative (−). No authors reviewed their own papers.

BvdM extracted data of individual studies, using a data extraction form, which was composed by using templates from the Cochrane association and the ADA. The data extraction form contained all fields that were considered relevant to address our study aim, such as study eligibility, reason for exclusion, quality rating, details on study design, results per outcome parameter, statistical methods, author’s conclusions and reviewer’s comments.

Following the quality appraisals, all team members summarized and assessed the strength of the evidence per outcome parameter. The evidence summary was created by adding up the numbers of studies and number of patients reporting a beneficial, negative or no effect on an outcome parameter. The number of good, neutral and negative quality studies was also documented in this summary. Consecutively, the ADA additional levels of evidence and grades for recommendations for developers of guidelines were used to grade the evidence. The ADA grading system for recommendations has been developed to assist guideline developers in assessing the entire body of evidence and indicating the strength of each guideline recommendation. According to the ADA system, RCTs and meta-analyses obtain a class A’ evidence. The ADA grading system was also documented in this summary.

Members of the expert team reached consensus on the strength of the evidence and the evidence statements for effects on outcome, summary. Consecutively, the ADA additional levels of evidence and grades for recommendations for developers of guidelines were used to grade the evidence. The ADA grading system for recommendations has been developed to assist guideline developers in assessing the entire body of evidence and indicating the strength of each guideline recommendation. According to the ADA system, RCTs and meta-analyses obtain a class A’ evidence. The ADA grading system was also documented in this summary.

Members of the expert team reached consensus on the strength of the evidence and the evidence statements for effects on outcome.
parameters. The team resolved conflicting appraisals by discussion and consensus.

**Results**

**Included studies**

Fifteen RCTs in relation to n-3 PUFA administration in patients with cancer were retrieved (Table 2). The quality of studies differed: nine studies were rated as positive quality21–24,26,37,43–45, five as neutral quality36,46–49 and one as negative quality38.

Five studies included patients with unintentional, self-reported, weight loss of more than 5%43,44,46 or more than 10%43. Two studies excluded either patients who reported ≥10% of unintentional weight loss over the previous 3 months37 or patients with severe malnutrition, as assessed by the Subjective Global Assessment (SGA) tool for malnutrition49. One study did not report details on nutritional status47, and the remaining studies only reported on the percentage of patients who had malnutrition at baseline (8–50%) without selecting patients with severe weight loss. However, these studies used various methods to identify malnutrition (see Table 2)22,23,26,43,46.

n-3 PUFAs were supplemented via (fish oil) capsules (0.3–4 g EPA)22,24,36–38,47,48, ONSs (2–2.3 g EPA)24,43–45,49 or tube feeding (2.3–6 g EPA)23,46. One study prescribed ONS preoperatively and tube feeding postoperatively (2.3 g EPA)26.

**Fish oil capsules**

This paragraph describes the design of the seven RCTs supplementing n-3 PUFAs by fish oil capsules, of which the quality was graded to be positive22,23,37, neutral36,47,48 and negative38 (Table 2). A number of studies have been conducted in

**Supplementary Table 1** Example of search strategy in PubMed®; effects of enteral supplementation of n-3 PUFA on clinical outcome in cancer

<table>
<thead>
<tr>
<th>PubMed® search</th>
<th>Medical subject headings and keywords</th>
<th>Limits: humans and English language</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>n-3 PUFA</td>
<td></td>
<td>41215</td>
</tr>
<tr>
<td>#2</td>
<td>Cancer</td>
<td></td>
<td>844623</td>
</tr>
<tr>
<td>#3</td>
<td>enteral* OR supplement* OR sip OR feed OR formula* OR liquid OR tube OR nasogastric OR nasojejunal OR nasoduodenal OR gastrostomy OR jejunostomy OR Enteral Nutrition* [MeSH]</td>
<td></td>
<td>132837</td>
</tr>
<tr>
<td>#5</td>
<td>“Postoperative Complications” [MeSH] OR complications OR complication* OR “morbidity” [MeSH] OR morbidity*</td>
<td></td>
<td>1119366</td>
</tr>
<tr>
<td>#6</td>
<td>“mortality” [MeSH terms] OR “hospital mortality” [MeSH terms] OR mortalit* OR death* OR survival OR “survival” [MeSH terms]</td>
<td></td>
<td>487681</td>
</tr>
<tr>
<td>#7</td>
<td>length of stay OR LOS OR “length of stay” [MeSH terms]</td>
<td></td>
<td>66749</td>
</tr>
<tr>
<td>#9</td>
<td>#4 OR #5 OR #6 OR #7 OR #8</td>
<td></td>
<td>1583988</td>
</tr>
<tr>
<td>#10</td>
<td>#1 AND #2 AND #3 AND #9</td>
<td></td>
<td>246</td>
</tr>
</tbody>
</table>

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Four small studies during chemotherapy have been described, of which three studies were non-blinded \cite{36,38,47} and one was double-blinded \cite{37}. In a Japanese study, 16 patients undergoing chemotherapy and allogeneic bone marrow transplantation were randomized to receive oral EPA three times daily, or no capsules \cite{47}. Another study randomized 23 patients with colorectal cancer: Intervention patients were offered four fish oil capsules per day (total 600 mg EPA + DHA) and the control group did not receive any supplements \cite{38}. Bonatto and colleagues performed an 8-week intervention of 2 g fish oil per day in 38 patients receiving chemotherapy after cancer surgery; control patients did not receive any supplements \cite{38}. Finocchiaro and colleagues studied 33 patients with advanced non-small cell lung cancer undergoing chemotherapy, randomized to receive four capsules (510 mg EPA and 340 mg DHA) or placebo capsules \cite{37}.

In these seven RCTs, loss to follow-up of patients varied from 7% to 50% \cite{21,22,36,37,48} or was not reported \cite{38,47}. Adherence with the fish oil capsules was established by plasma fatty acids or diaries \cite{21,37,48} or not reported \cite{22,36,38,47}. Oral nutritional supplements containing n-3 PUFAs

We identified five RCTs investigating the effects of ONS containing n-3 PUFAs in patients with cancer, most of positive quality \cite{24,43-45} and one of negative quality \cite{49}. In a large double-blind study, 200 weight-losing pancreatic cancer patients were randomized to receive n-3 PUFA-containing ONS or an isonitrogenous control ONS \cite{24}. In a small subgroup \((n = 24)\) of this study, Moses and colleagues investigated resting energy expenditure (REE) by indirect calorimetry as well as total energy expenditure (TEE) by doubly labelled water \cite{23}. Two studies investigated n-3 PUFA-containing ONS

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**Figure 1:** Flow chart of systematic literature search
Table 2  Summary of randomized controlled trials on the role of EPA in patients with cancer

| Author, year | Study design | Aim | Study population | Intervention | Outcomes | Conclusions
<table>
<thead>
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<tbody>
<tr>
<td>Gogos et al. 1998</td>
<td>Non-blinded RCT</td>
<td>To investigate the effect of n-3 PUFA plus vitamin E on the immune status and survival of well-nourished and malnourished patients with generalized malignancy</td>
<td>64 patients with mixed solid tumour types (prevalence of malnutrition at baseline: 50%)</td>
<td>40 days E: n = 30 18 g/day fish oil capsules (max-EPA, 3.06 g EPA + 2.07 g DHA) C: n = 30 18 g/day placebo capsules</td>
<td>Four patients (6.7%) dropped out of the study because of poor adherence Energy intake—NA Protein intake—NA Weight—ns improvement FFM—NA Functional capacity—KPS after 40 days in malnourished patients receiving fish oil only Quality of life—NA Survival—increase in E group only (P &lt; 0.025 compared with C) Other—no effect of fish oil on albumin or transferrin. No toxicity of fish oil except for mild abdominal discomfort and transient diarrhoea</td>
<td>n-3 PUFA seemed to prolong survival and improve KPS in malnourished patients with generalized malignancy</td>
</tr>
<tr>
<td>Takatsuka et al. 2001</td>
<td>Non-blinded RCT</td>
<td>To assess the effectiveness of prophylactic oral EPA therapy in preventing complications in patients who received bone marrow transplantation</td>
<td>n = 16 patients undergoing chemotherapy and allogeneic bone marrow transplantation from unrelated donors (details on nutritional status not provided)</td>
<td>21 days before to 180 days after bone marrow transplantation E: n = 7 capsules (1.8 g EPA) C: n = 9 no capsules</td>
<td>Zero dropouts reported Energy intake—NA Protein intake—NA Weight—NA FFM—NA Functional capacity—NA Quality of life—NA Survival—higher survival rate in E group (E: n = 0 died vs. C: n = 5 died) (P &lt; 0.01) Other—reduced complications in E group (E: n = 3 graft-vs.-host disease, n = 4 no complications vs. C: n = 6 graft-vs.-host disease, n = 4 thrombotic microangiopathy, n = 4 CMV disease)</td>
<td>Survival rate was significantly higher in the group given EPA, and EPA significantly reduced the complications of BMT</td>
</tr>
<tr>
<td>Bruera et al. 2003</td>
<td>Double-blinded RCT</td>
<td>To determine whether high doses of fish oil, administered over 2 weeks, improve symptoms in patients with advanced cancer</td>
<td>87 advanced cancer patients (&gt; 5% weight loss)</td>
<td>2 weeks E: n = 30 fish oil capsules (mean EPA 1.8 g) C: n = 30 placebo capsules</td>
<td>Sixty patients completed the study (dropout 31%) Twenty-seven patients (31%) did not complete the study Energy intake—NA Protein intake—NA Weight—NA Functional capacity—KPS ↑ 10.0 E vs. ↓ 6.9 C</td>
<td>No effects on outcome parameters after 2 weeks of n-3 PUFA supplementation Nonadherence with protocol in both groups 10%</td>
</tr>
</tbody>
</table>
Table 2 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Interventions</th>
<th>Outcome Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fearon et al. 2006&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Double-blinded RCT Positive</td>
<td>To compare EPA diethyl ester with placebo in cachectic cancer patients for effects on weight and fat-free mass in patients with advanced cancer</td>
<td>n = 518 upper/lower gastrointestinal and lung cancer patients (≥5% weight loss) 8 weeks E1: n = 175: 95% diester (2 g EPA) E2: n = 172: 95% diester (4 g EPA) C: n = 171: placebo At week 8, 270 patients remained (dropout 48%) Energy intake—NA Protein intake—NA Weight—↑1.2 kg (2 g EPA) vs. C; ↑0.3 kg vs. placebo (4 g EPA), P = 0.066 FFM—2 g EPA: 0.9 kg vs. C; 4 g EPA: −0.1 vs. C (ns) Functional capacity—KPS, weakness (ns) Physical function and KPS—ns Quality of life—2 g EPA: ↑4.3 physical functioning; 4 g EPA: −3.4 (P = 0.04) Survival—2 g EPA: 155 days; 4 g EPA: 142 days; C: 140 days (ns) Other—appetite, albumin, CRP, nausea, vomiting, diarrhoea (ns), supplements were well tolerated, adverse events (ns), serious adverse events not related to supplements</td>
</tr>
<tr>
<td>Finocchiaro et al. 2011&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Double-blinded RCT Positive</td>
<td>To investigate the effect of EPA and DHA vs. placebo on inflammatory condition and oxidative and nutritional statuses</td>
<td>n = 33 patients with lung cancer (patients with ≥10% weight loss over the previous 3 months were excluded) 66 days E: n = 19 4 fish oil capsules (510 mg EPA + 310 mg DHA) C: n = 14 4 olive oil capsules (850 mg) Twenty-seven patients completed the study (E: n = 13, C: n = 14), adherence was good Energy intake—ns between groups Protein intake—ns between groups Weight—E increase of 3.4 kg (P &lt; 0.05 vs. baseline), C stable, ns between groups FFM—NA Functional capacity—NA Quality of life—NA Survival—NA Other—albumin, thyroxin-binding prealbumin and transferrin: ns between groups, CRP and IL-6 after 66 days lower in E than C group (P &lt; 0.05) Increase in body weight in the n-3 group; reduction in inflammatory indexes and oxidative status Small sample size, no data on FFM or quality of life</td>
</tr>
<tr>
<td>Bonatto et al. 2011&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Non-blinded RCT Negative</td>
<td>To investigate the effect of fish oil in patients receiving</td>
<td>n = 38 patients tumours at various sites (predominantly gastrointestinal) 8 weeks E: n = 19 fish oil capsules 2 g/ days (0.3 g EPA + 0.3 g DHA) Zero dropouts reported Energy intake—NA Protein intake—NA Weight—E increase of 3.4 kg (P &lt; 0.05 vs. baseline), C stable, ns between groups FFM—NA Functional capacity—NA Quality of life—NA Survival—NA Other—albumin, thyroxin-binding prealbumin and transferrin: ns between groups, CRP and IL-6 after 66 days lower in E than C group (P &lt; 0.05) Fish oil prevented the decline in neutrophil number and increase in body weight in the n-3 group; reduction in inflammatory indexes and oxidative status Small sample size, no data on FFM or quality of life</td>
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</table>

The results indicate no significant benefit from single-agent EPA in the treatment of cancer cachexia.

Fearon et al. 2006<sup>21</sup>

Double-blinded RCT

Positive

To compare EPA diethyl ester with placebo in cachectic cancer patients for effects on weight and fat-free mass in patients with advanced cancer

n = 518 upper/lower gastrointestinal and lung cancer patients (≥5% weight loss) 8 weeks E1: n = 175: 95% diester (2 g EPA) E2: n = 172: 95% diester (4 g EPA) C: n = 171: placebo At week 8, 270 patients remained (dropout 48%) Energy intake—NA Protein intake—NA Weight—↑1.2 kg (2 g EPA) vs. C; ↑0.3 kg vs. placebo (4 g EPA), P = 0.066 FFM—2 g EPA: 0.9 kg vs. C; 4 g EPA: −0.1 vs. C (ns) Functional capacity—KPS, weakness (ns) Physical function and KPS—ns Quality of life—2 g EPA: ↑4.3 physical functioning; 4 g EPA: −3.4 (P = 0.04) Survival—2 g EPA: 155 days; 4 g EPA: 142 days; C: 140 days (ns) Other—appetite, albumin, CRP, nausea, vomiting, diarrhoea (ns), supplements were well tolerated, adverse events (ns), serious adverse events not related to supplements

The results indicate no significant benefit from single-agent EPA in the treatment of cancer cachexia.

Finocchiaro et al. 2011<sup>37</sup>

Double-blinded RCT

Positive

To investigate the effect of EPA and DHA vs. placebo on inflammatory condition and oxidative and nutritional statuses

n = 33 patients with lung cancer (patients with ≥10% weight loss over the previous 3 months were excluded) 66 days E: n = 19 4 fish oil capsules (510 mg EPA + 310 mg DHA) C: n = 14 4 olive oil capsules (850 mg) Twenty-seven patients completed the study (E: n = 13, C: n = 14), adherence was good Energy intake—ns between groups Protein intake—ns between groups Weight—E increase of 3.4 kg (P < 0.05 vs. baseline), C stable, ns between groups FFM—NA Functional capacity—NA Quality of life—NA Survival—NA Other—albumin, thyroxin-binding prealbumin and transferrin: ns between groups, CRP and IL-6 after 66 days lower in E than C group (P < 0.05) Increase in body weight in the n-3 group; reduction in inflammatory indexes and oxidative status Small sample size, no data on FFM or quality of life

The results indicate no significant benefit from single-agent EPA in the treatment of cancer cachexia.

Bonatto et al. 2011<sup>38</sup>

Non-blinded RCT

Negative

To investigate the effect of fish oil in patients receiving

n = 38 patients tumours at various sites (predominantly gastrointestinal) 8 weeks E: n = 19 fish oil capsules 2 g/ days (0.3 g EPA + 0.3 g DHA) Zero dropouts reported Energy intake—NA Protein intake—NA Weight—E increase of 3.4 kg (P < 0.05 vs. baseline), C stable, ns between groups FFM—NA Functional capacity—NA Quality of life—NA Survival—NA Other—albumin, thyroxin-binding prealbumin and transferrin: ns between groups, CRP and IL-6 after 66 days lower in E than C group (P < 0.05) Fish oil prevented the decline in neutrophil number and increase in body weight in the n-3 group; reduction in inflammatory indexes and oxidative status Small sample size, no data on FFM or quality of life

The results indicate no significant benefit from single-agent EPA in the treatment of cancer cachexia.

### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Endpoint</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silva et al. 2012&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Non-blinded RCT Neutral</td>
<td>To check whether there is a change in the markers of inflammation and/or nutritional status of patients with colorectal cancer undergoing chemotherapy who were supplemented with 2 g of fish oil, compared with the non-supplemented ones</td>
<td>n = 23 patients with colorectal cancer in chemotherapy treatment (prevalence of malnutrition at baseline: 0 %, according to BMI, 52.2% lost &gt; 5% and 26.1% lost &gt; 10%)</td>
<td>9 weeks, during chemotherapy (starting at the first day of chemotherapy) E: n = 11 2 g fish oil capsules (four capsule, 200 mg EPA + DHA per capsule) C: n = 12 capsules</td>
<td>Five individuals did not complete the study (1 E, 4 C) Energy intake—NA Protein intake—NA Weight—E + 1.7 kg, C—2.5 kg (P &lt; 0.002 for difference between groups) FFM—NA Functional capacity—NA Quality of life—NA Survival—NA Other</td>
</tr>
<tr>
<td>Fearon et al. 2003&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Double-blinded RCT Positive</td>
<td>To compare a protein and energy-dense supplement enriched with n-3 PUFA and antioxidants with an isocaloric isonitrogenous control supplement for effects on weight, FFM, dietary intake and quality of life in cachectic patients with advanced pancreatic cancer</td>
<td>Two hundred untreated pancreatic cancer patients (&gt;5% weight loss over the previous 6 months)</td>
<td>8 weeks E: n = 95 high protein and energy ONS + 2.2 g EPA + 0.9 g DHA C: n = 105 isonitrogenous control ONS</td>
<td>Around 110 patients completed the study (dropout 45%) Energy intake—↑224 kcal E vs. 68 kcal C (ns); significant ↑ E baseline to 8 weeks only Protein intake—↑15 g E vs. 6 g C (ns); significant ↑ E baseline to 8 weeks only Weight—↓0.37 kg E vs. ↓0.25 kg C (ns); significant change in baseline to 8 weeks E and C; weight ↑ correlated with intake cans E only FFM—↑0.27 E vs. 0.12 C (ns); ↑ FFM correlated intake cans E only Functional capacity Physical function and KPS—ns Quality of life—Global E vs. C (ns); post-hoc analysis ↑ QoL and ↑ weight E only Survival—142 days E vs. 128 days C (ns) Other—ONSs were well tolerated, adverse events (ns), serious adverse events not related to study supplements</td>
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</table>

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To investigate the effects of an ONS containing n-3 PUFA on TEE, REE and PAL in home-living cachectic patients with advanced pancreatic cancer

Eight weeks

E: n = 9 high protein and energy ONS + 2.2 g EPA + 0.9 g DHA
C: n = 15 isonitrogenous control ONS

Five patients did not complete the study (E: n = 3, C: n = 2).

Adherence: mean intake E: 1.9 cans/day, C: 1.5 cans/day (ns)

Energy intake—increased significantly in E patients compared with baseline intake, trend when compared with C patients

Protein intake—increased significantly in E patients compared with baseline intake, trend when compared with C patients

Weight—ns

FFM—ns

Functional capacity—NA

Quality of life—NA

Survival—NA

Other—REE, TEE and PAL of C patients did not change significantly; TEE and PAL of E patients increased significantly, REE did not change; no significant differences between groups

Administration in EPA-containing ONS was associated with an increase in PAL

<table>
<thead>
<tr>
<th>Table 2 (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moses et al. 2004</strong>&lt;sup&gt;44&lt;/sup&gt; Double-blinded RCT Positive</td>
</tr>
<tr>
<td>To investigate the effects of an ONS containing n-3 PUFA on TEE, REE and PAL in home-living cachectic patients with advanced pancreatic cancer</td>
</tr>
<tr>
<td>n = 24 patients with advanced pancreatic cancer (&gt;5% weight loss over the previous 6 months)</td>
</tr>
<tr>
<td>8 weeks</td>
</tr>
<tr>
<td>E: n = 9 high protein and energy ONS + 2.2 g EPA + 0.9 g DHA</td>
</tr>
<tr>
<td>C: n = 15 isonitrogenous control ONS</td>
</tr>
<tr>
<td>Five patients did not complete the study (E: n = 3, C: n = 2). Adherence: mean intake E: 1.9 cans/day, C: 1.5 cans/day (ns) Energy intake—increased significantly in E patients compared with baseline intake, trend when compared with C patients Protein intake—increased significantly in E patients compared with baseline intake, trend when compared with C patients Weight—ns FFM—ns Functional capacity—NA Quality of life—NA Survival—NA Other—REE, TEE and PAL of C patients did not change significantly; TEE and PAL of E patients increased significantly, REE did not change; no significant differences between groups Administration in EPA-containing ONS was associated with an increase in PAL</td>
</tr>
</tbody>
</table>

| **Guarcello et al. 2007**<sup>43</sup> Non-blinded RCT Positive |
| To evaluate the influence of an EPA-enriched, energy-dense oral supplement on inflammatory and nutritional status, as well as on the quality of life of lung cancer patients |
| n = 46 lung cancer patients undergoing chemotherapy (>10% weight loss over the previous 6 months) |
| 60 days |
| E: n = 26 high protein and energy ONS + 2.2 g EPA + 1.0 g DHA |
| C: n = 20 isocaloric ONS |
| Twenty-five patients completed the study (dropout rate 45.7%) Energy intake—E: ↑ 700 kcal (P < 0.05 vs. baseline) vs. C: ↑ 170 kcal Protein intake—E: ↑ 20 g (P < 0.05 vs. baseline) vs. C: ↑ 4.4 g Weight—increase in E (E: ↑ 0.9 kg (P < 0.05 vs. baseline), C: ↑ 0.0 kg FFM—NA Functional capacity—NA Quality of life—functional status E: ↑ 13.3 vs. C: ↑ 10, symptom scale EPA: ↓ 12.8 vs. C: ↓ 6.5 (P < 0.05 vs. baseline) Survival—ns Other—E: appetite after 30 days: ↑ 2 (P < 0.05 vs. baseline), C ↑ 1 (ns), ONSs were well tolerated |

| **van der Meij et al. 2011**<sup>15, 2012</sup> Double-blinded RCT Positive |
| To investigate the effects of an ONS containing n-3 PUFA on nutritional status and inflammatory markers in patients with stage III NSCLC |
| n = 40 patients with lung cancer undergoing chemoradiotherapy (prevalence of malnutrition at baseline: 20%) Definition of malnutrition: |
| 5 weeks |
| E: n = 20 high protein and energy ONS + 2.02 g EPA + 0.92 g DHA |
| C: n = 20 isocaloric control ONS |
| Seven patients did not complete the study (dropout rate 17.5%). Adherence: mean dose ~1 pack/day (1.1 g EPA) Energy intake—E ↑ 2,456 kJ vs. C after 4 weeks (P = 0.03) Protein intake—E ↑ 12.4 g (P = 0.08), ↑ 25.0 g (P = 0.01) vs. C after 1 week and 4 weeks Weight—E better weight |

ONS containing n-3 PUFA seems effective in improving the nutritional status and quality of life of lung cancer patients undergoing chemotherapy Increase in time in n-3 group reported, no differences between groups reported A protein- and energy-dense ONS containing n-3 PUFA beneficially affects nutritional status during multimodality treatment in
Table 2 (Continued)

| Undergoing multimodality therapy, Secondary effect parameters included quality of life and functional status | >5% weight loss over the previous month, >10% weight loss over the previous 6 months or BMI < 18.5 | Maintenance than C after 1, 2 and 4 weeks ↑ 1.1 kg (P = 0.07), ↑ 1.3 kg (P = 0.02), ↑ 1.7 kg (P = 0.04) FFM—E less decrease vs. C, difference: 1.5 kg (P = 0.05), 1.9 kg (P = 0.02) after 3 and 5 weeks Functional capacity—KPS E ↑ 3.5 vs. C after 3 weeks (P = 0.02) Quality of life—physical and cognitive function E ↑ 11.6 and ↑ 20.7 (P < 0.01) vs. C; global health status E ↑ 12.2 and social function ↑ 22.1 vs. C (P = 0.04) Survival—NA Other—physical activity: E ↑ 6.6 (P = 0.04), ↑ 2.5 (P = 0.05) vs. C after 3 and 5 weeks REE: E ↓ 16.7% of predicted (P = 0.01), ↓ 4 kJ/kg (P = 0.07) vs. C after 3 weeks | Patients with NSCLC Average consumption of study ONS during chemoradiotherapy was approximately 1 can/d (1 g EPA) |

Trabal et al. 2010 Non-blinded RCT Neutral

To assess the effect of an intervention with an EPA-ONS on chemotherapy tolerability in patients with advanced colorectal cancer

n = 13 patients with stage IV colorectal cancer that were going to receive first-line chemotherapy treatment (severely malnourished patients according to SGA were excluded)

12 weeks

E: n = 5 high protein and energy ONS + 2 g EPA + 0.9 g DHA + dietary counselling

C: n = 6 dietary counselling

Two patients (15.4%) did not complete the study. Adherence: mean dose 1.6 packs/day (1.6 g EPA) Energy intake—E group consumed on average 312 kcal more than C group (ns between groups) Protein intake—E group consumed on average 18 g protein more than C group (ns between groups) Weight—E group weight gain +4.94 kg vs. –1.17 kg (C), P = 0.045 FFM—NA Functional capacity—NA Quality of life—GHS/QoL scale—E: 3.33 vs. C: –6.94 (ns) Physical function: –4 vs. –15.56 (ns) Role function—E: 13.33 vs. 2.78 (ns) Social function—E: 16.67 vs. C: –13.89; P = 0.038 Fatigue—E: –4.44 vs. C: 11.11 (ns) Pain—E: –10 vs. 2.78 (ns) Loss of appetite—E: 6.67 vs. C: –16.67 (ns) Survival—NA

Improvement in weight gain and some important domains of QoL in advanced colorectal cancer patients taking EPA-containing ONS plus dietary counselling Small sample size, no EPA vs. control ONS
**Table 2 (Continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Objective</th>
<th>Patients</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenler et al. 1996&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Double-blinded RCT</td>
<td>Neutral</td>
<td>n = 50 patients with upper gastrointestinal cancer (prevalence of malnutrition at baseline: 48%)</td>
<td>Definition of malnutrition: MUAMC &lt;10&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>7 days postoperative: n = 17 n-3 PUFA/MCT tube feeding (4.0 g EPA; 1.9 g DHA) n = 18 isocaloric, isonitrogenous control tube feeding</td>
</tr>
<tr>
<td>Ryan et al. 2009&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Double-blinded RCT</td>
<td>Positive</td>
<td>n = 70 oesophageal cancer patients (prevalence of mild, moderate or severe malnutrition at baseline: 63%, &gt;10% weight loss: 19%)</td>
<td>Definition of malnutrition: NRI (combining serum albumin and weight loss)</td>
<td>5 days postoperative (ONS): n = 28 high protein and energy ONS or tube feeding + 2.3 g EPA + 1.0 g DHA C: n = 25 isocaloric control ONS or tube feeding</td>
</tr>
</tbody>
</table>

Other chemotherapy adherence: none of five E patients had to delay or stop their chemotherapy; four of six control patients experienced toxicity and interruption (ns); routine laboratory parameters (ns)
interventions in patients with lung cancer: Guarcello and colleagues compared the effects of n-3 PUFA-containing ONS with an isocaloric, isonitrogenous control ONS. van der Meij and colleagues compared the effects of an n-3 PUFA-containing ONS with an isocaloric, isonitrogenous control ONS. The first trial administered n-3 PUFA-containing ONS 5 days preoperatively and n-3 PUFA-containing tube feeding during 21 days postoperatively. In the second large trial, n-3 PUFA-containing enteral nutrition, or an isonitrogenous control enteral nutrition, was administered 7 days before and after surgery. A third group only received standard enteral nutrition during 7 days postoperatively. A smaller study performed a relatively short (7 days) postoperative intervention with n-3 PUFA-containing enteral nutrition in 50 patients with upper GI cancer.

Dropout rates of 12%23, 24%26 and 30%46 were reported, and due to tolerance issues, enteral nutrition goals were not always reached in two studies23,46. One study did not specify blinding and randomization methods46. One study, although of high quality, did not report between-group differences for body weight and fat-free mass, but only within-group differences over time26.

Strength of the evidence

Appetite
It is suggested that n-3 PUFAs reduce the inflammatory response, thereby improving appetite. In five studies, n-3 PUFAs did not affect appetite

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when compared with controls (van der Meij 2012 +, Fearon 2003 +, Trabal Ø, Fearon 2006 +, Bruera Ø) (total n = 858)\textsuperscript{21,24,45,48,49}. One positive quality study found an improvement in appetite over time (30 days, though not after 60 days) in patients with lung cancer receiving n-3 PUFA ONS, but not in control patients (n = 46, Guarcello +)\textsuperscript{41}.

**Recommendation**

n-3 PUFA supplementation does not improve appetite (grade II).

**Energy and protein intake**

Energy intake was reported in seven studies (n = 443, Fearon 2003 +, van der Meij 2010 +, Finocchiaro +, Guarcello +, Moses +, Bruera Ø, Trabal Ø)\textsuperscript{24,37,43–45,48,49} and protein intake in six studies (n = 356; Fearon 2003 +, van der Meij 2010 +, Finocchiaro +, Guarcello +, Moses +, Bruera Ø)\textsuperscript{24,37,43–45,48}. There was no significant increase in energy\textsuperscript{48} or both energy and protein intake with n-3 PUFAs (capsules or ONS) compared with a control supplement (n = 373, Fearon 2003 +, van der Meij 2010 +, Finocchiaro +, Bruera Ø, Trabal Ø)\textsuperscript{24,37,43–45,48,49}. One study reported within-group clinically meaningful improvements in energy and protein intake with an n-3 PUFA ONS, but not in the group receiving the control ONS (+700 kcal/day and +20 g protein/day vs. +170 kcal/day and +4.5 g protein/day) (n = 46, Guarcello +)\textsuperscript{30}, and one study reported improved protein intake in patients receiving the n-3 PUFA-containing ONS (+27 g/day vs. control + 4 g/day) (n = 24, Moses +)\textsuperscript{44}.

**Recommendation**

There is no evidence that n-3 PUFA supplementation influences energy and protein intake (grade II).

**Body weight**

Results from 12 studies show equivocal effects on stabilization or improvement of body weight after supplementation of n-3 PUFAs in cancer patients: five studies did not find significant differences between n-3 and control groups (n = 570, Fearon 2003 +, Moses +, Gogos +, Sultan +, Bruera Ø); one study observed a tendency for body weight maintenance in the n-3 PUFA group receiving 2 g EPA by diester emulsion, as compared with groups receiving 4 g EPA or a placebo emulsion (n = 518, Fearon 2006 +)\textsuperscript{21}; three studies observed a significant body weight maintenance in the n-3 PUFA group versus a control intervention (n = 91, van der Meij 2010 +, Trabal Ø, Bonatto –)\textsuperscript{38,45,49}; and three studies demonstrated a within-group weight maintenance over time in the n-3 PUFA group (n = 102, Silva Ø, Guarcello +, Finocchiaro Ø)\textsuperscript{36,37,43}.

**Recommendation**

The effects of n-3 PUFA supplementation on body weight maintenance are inconclusive (grade II).

**Fat-free mass**

Five studies measured the effect of an n-3 PUFA ONS on fat-free mass. Three studies did not observe difference for fat-free mass as compared with a control intervention (n = 742, Fearon 2006 +, Fearon 2003 +, Moses +)\textsuperscript{21,33,44}. One study observed a better maintenance of fat-free mass in patients with lung cancer receiving n-3 ONS, as compared with a control ONS (n = 40, van der Meij 2010 +)\textsuperscript{45}, and one study observed a maintenance of fat-free mass over time in patients receiving n-3 PUFA-containing ONS and enteral nutrition around oesophageal cancer surgery (n = 70, Ryan +)\textsuperscript{26}.

**Recommendation**

The effects of n-3 PUFA supplementation on fat-free mass are inconclusive (grade II).

**Karnofsky performance status**

Two large studies reported no improvements in Karnofsky performance status with n-3 PUFAs (n = 605, Fearon 2006 +, Bruera Ø)\textsuperscript{21,44}. However two smaller positive quality studies (n = 104, van der Meij 2012 +, Gogos +)\textsuperscript{22,50} reported improvements in Karnofsky performance status.

**Recommendation**

The effects of n-3 PUFA supplementation on Karnofsky performance status are inconclusive (grade II).

**Quality of life**

ONS containing n-3 PUFAs improved global health status, physical, cognitive, and social function compared with a control intervention in a small study (n = 40, van der Meij 2012 +)\textsuperscript{36}; another small study only observed a significant improvement in social function in the n-3 PUFA group, not in other quality-of-life parameters (n = 13, Trabal Ø)\textsuperscript{40}; one large study found a trend for improved physical function in patients receiving 2 g EPA by a diester emulsion, compared with 4 g EPA or a placebo (n = 518, Fearon 2006 +)\textsuperscript{21}; and one small study found reduced tiredness to be correlated with the n-3 PUFA dose (n = 87, Bruera Ø)\textsuperscript{46}. A small study observed a within-group improvement of functional status and symptom scores over time in the n-3 PUFA group (n = 46, Guarcello +)\textsuperscript{30}. A large positive trial did not find significant differences for quality-of-life parameters (n = 200, Fearon 2003 +)\textsuperscript{24}.

**Recommendation**

n-3 PUFA supplementation has modest beneficial effects on some aspects of quality of life (grade II).

**Physical activity level**

Two small studies investigated the effects of n-3 PUFA-containing ONS on parameters of physical activity (n = 64, Moses +, van der Meij 2012 +)\textsuperscript{14,59}.

In one study in pancreatic cancer patients, TEE (measured by doubly labelled water) increased after 8 weeks in the group receiving the n-3
PUFA-containing ONS, not in the control group\(^4\). The second study was performed in lung cancer patients. Physical activity assessed by an accelerometer was higher in patients with lung cancer receiving n-3 PUFA ONS during 5 weeks of chemoradiotherapy\(^5\).

**Recommendation**

n-3 PUFA supplementation appears to have beneficial effects on physical activity in patients with cancer (grade III).

**Complications**

In one small neutral quality study, n-3 PUFA capsules reduced complication rate in bone marrow transplant (BMT) patients \((n = 16,\) Takatsuka \(\varnothing)\)\(^4\). Three studies investigated the effects of a single n-3 PUFA intervention in the absence of multiple immune-enhancing compounds around cancer surgery. One study observed a significant reduction in infections in the n-3 PUFA group \((n = 50,\) Kenler \(\varnothing)\)\(^5\), contrary to a large study that did not observe differences for infectious complications \((n = 195,\) Sultan \(\varnothing)\)\(^5\). Furthermore, there were no effects of n-3 PUFAs (by ONSs and/or tube feeding) on major complications \((n = 248,\) Ryan \(\varnothing,\) Sultan \(\varnothing)\)\(^5\). Among the seven studies supplementing n-3 PUFA by capsules \((n = 661)\), two studies observed GI side effects in the n-3 PUFA group slightly more frequently than in the control group \((P \text{ value not reported}) \((n = 120,\) Bruera \(\varnothing,\) Finocchiaro \(\varnothing)\)\(^5\). Another study reported adverse events in n-3 PUFA and control groups; no serious adverse events were related to the study capsules \((n = 518,\) Fearon 2006 \(\varnothing)\)\(^5\). Furthermore, in one small study, no side effects related to fish oil capsules were reported \((n = 23,\) Silva \(\varnothing)\)\(^5\).

In studies applying n-3 PUFA-containing ONS (five studies, \(n = 299)\), two studies reported adverse events in both groups and no serious adverse events related to n-3 PUFA \((n = 240,\) Fearon 2003 \(\varnothing,\) van der Meij 2010 \(\varnothing)\)\(^5\). Another study reported excellent tolerance of the n-3 PUFA-containing ONS \((n = 46,\) Guarcello \(\varnothing)\)\(^5\). Others reported chemotherapeutic effects in both n-3 PUFA and control groups, but numbers were too small to test for statistical significance \((n = 53,\) Trabal \(\varnothing,\) van der Meij 2012 \(\varnothing)\)\(^5\). In studies using enteral nutrition in upper GI surgery patients, GI complaints and intolerance to the enteral nutrition were similar in n-3 PUFA and control groups \((n = 315,\) Ryan \(\varnothing,\) Sultan \(\varnothing,\) Kenler \(\varnothing)\)\(^5\). One study reported minor GI complaints (no serious adverse events) in both n-3 and control groups \((n = 70,\) Ryan \(\varnothing)\)\(^5\) and another study observed slightly more GI complaints in the control group \((P \text{ value not reported},\) \(n = 50,\) Kenler \(\varnothing)\)\(^5\). In one study, only 50% of the overall study population reached the aimed feeding rate owing to problems with tolerance and/or complications, such as diarrhoea, ileus, nausea, vomiting or bloating \((n = 195,\) Sultan \(\varnothing)\)\(^5\).

**Recommendations**

n-3 PUFA supplementation by capsules or ONS appears to be safe to administer in cancer patients receiving chemo(radio)therapy or palliative care (grade II).

Intolerance to enteral nutrition around upper GI cancer surgery does not appear to be related to n-3 PUFAs (grade II).

**Discussion**

The authors have referenced some of their own studies in this systematic review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

This literature review gives an up-to-date overview on the available evidence for the effects of n-3 PUFAs on clinical outcome parameters in patients with cancer. We conclude that fair evidence shows that supplementation of n-3 PUFA appears to be safe and may improve the quality of life and physical activity. However, supplementation of n-3 PUFA does not influence energy or protein intake, appetite, or survival in cancer.
Patients. Effects on body weight, fat-free mass and performance status are equivocal: around half of studies find beneficial effects while others do not show differences compared with control interventions. Moreover, fair evidence shows that supplementation does not reduce postoperative complications.

These conclusions were drawn after a systematic qualitative evidence analysis of studies published until April 2013, carried out by an international expert team. In order to objectively evaluate the effects of n-3 PUFAs in cancer, a meta-analysis on this subject is required, but the variability in study designs makes it yet impossible to carry out meta-analyses. Also, some authors report between-group differences, whereas others only report within-group differences.

Thus far, conclusions from meta-analyses and systematic reviews on this topic were equivocal and did not strongly recommend supplementing n-3 PUFAs in patients with cancer. These reviews included studies published until 2005/2006. The current systematic review includes publications until April 2013, in this way providing a new update.

Supplementation of n-3 PUFAs appeared to be safe, but the way in which they interact with anticancer treatment needs to be further unravelled. EPA and DHA can inhibit tumour growth through apoptosis, inhibition of angiogenesis, and alterations to cell signalling. An improved response to chemotherapy by n-3 PUFAs has also been observed in clinical studies in patients with lung and breast cancer. In most included RCTs, chemotherapy outcomes in patients who received n-3 PUFAs appeared to be comparable with control patients. On the contrary, findings from a study in mice found that platinum-induced PUFAs, metabolites of n-3 PUFAs from algae and fish oil, were involved in the resistance to platinum-based chemotherapy. Supplements containing pure EPA did not cause chemotherapy resistance. It is yet unclear if these metabolites are abundant in all n-3 PUFA supplements, and if the same resistance occurs in humans. As such, it might be oversimplified to discourage dietary n-3 PUFAs in patients with cancer. When supplementation of n-3 PUFAs during chemotherapy is considered, it is recommended to use purified n-3 PUFA supplements instead of less refined whole fish oil or algae supplements, and to carefully assess patients chemotherapy outcomes in future trials investigating n-3 PUFA supplements.

A limitation of this review is the heterogeneity of the 15 available studies. The trials differed in terms of patient populations, inclusion and exclusion criteria, intervention strategies and study durations. The administered dose ranged from 300 mg to 6 g of EPA, and in some studies, especially the studies with fish oil capsules, patient adherence with study supplements was not documented. In addition, the study populations are heterogeneous in terms of nutritional status and cachexia. Some studies selected patients on the degree of weight loss; others did not apply an inclusion criterion on nutritional status or cachexia. Some studies did not have adequate statistical power: around half of the studies were small (10 studies included 60 or fewer participants). The large studies had a high dropout rate (around 50%): this may also have biased the results.

Apart from immune-modulating effects of n-3 PUFAs in patients with cancer cachexia, additional energy and protein are required for body weight maintenance and synthesis of lean tissue. The effect of n-3 PUFAs combined with additive energy and protein on nutritional status is expected to be larger than the effect of a single n-3 PUFA intervention. Apart from the study of Trabal and colleagues, all included studies provided comparable amounts of energy and protein and nutritional counselling in both intervention and control groups. As a result, these studies investigated the pure effect of n-3 PUFAs, provided that both groups consumed a comparable amount of n-3 PUFAs by normal foods. None of the studies described the consumption of fish or other foods containing n-3 PUFAs, such as walnuts containing alpha-linolenic acid. Alternatively, only a few studies checked the plasma phospholipid EPA concentration as a measure of n-3 PUFA intake.

Study design is a limiting factor when addressing the evidence of n-3 PUFAs in cancer patients. The adherence to the study intervention was not always monitored; suboptimal adherence to n-3 PUFA supplements could have resulted in a lack of effect. Future trials should consider a choice of supplementation format (capsules or liquid), or the use of n-3 PUFA-containing enteral or parenteral nutrition, in order to improve patients’ adherence.

The nutritional parameters also differ between studies. Body weight is widely used but is unreliable in case of ascites or oedema and gives no information on body composition. Even so, bioelectrical impedance analysis to measure fat-free mass might be unreliable in patients with cancer. CT image analysis or dual-energy x-ray absorptiometry is preferred as the method to precisely quantify skeletal muscle. Ultimately, positive effects on body composition should be translated to improvements of quality of life. A few RCTs observed positive effects of n-3 PUFAs on both body weight and quality of life; the latter is more relevant to patients with cancer. Still, we need more large RCTs confirming this relationship.

Conventional nutritional interventions for cancer patients have limited effects on clinical endpoints or the quality of life during chemotherapy or palliative care. If supplementation of n-3 PUFAs does not
improve cancer cachexia parameters, such as body weight and quality of life, the effect is relatively small. Therefore, more benefits are expected from combination treatments including anticatabolic and orexigenic agents and n-3 PUFA\sech{61}. In a five-arm RCT in patients with cachexia, the combination regimen that included the administration of an appetite stimulant, ONS with EPA and DHA, L-carnitine, and thalidomide was shown to be the most effective treatment in terms of lean body mass, REE and fatigue\sech{62}. While promising, the lack of robust evidence suggests the need for large, welldesigned RCTs to confirm the efficacy of these treatments and to refine the optimal dosage and duration of administration. However, the evidence suggests beneficial effects of physical exercise training during chemotherapy, but a combination intervention of training and nutritional counselling or nutritional supplementation has yet to be studied. Rogers and colleagues are currently conducting an open-label, prospective RCT on EPA, the COX-2 inhibitor celecoxib, combined with leucine supplementation and resistance training\sech{63}. Nutritional interventions are often offered in patients with nutritional issues and weight loss; prophylactic nutritional intervention is not standard. New insights suggest that early nutritional intervention in patients with early-stage cachexia could be more effective than interventions in patients with advanced cancer cachexia, but to our knowledge, few studies on this topic have been published\sech{64–66}. Recently, a proposal for the definition of cancer cachexia has been published, and attention has been paid to the identification of patients with ‘pre-cachexia’ as a probable indication to start nutritional intervention\sech{67}. However, definitions of cachexia and pre-cachexia need to be validated and further refined.

**Conclusion**

This review helps clinicians to decide on the prescription of n-3 PUFAs in patients with cancer cachexia. There is increasing evidence that n-3 PUFAs are safe to administer to cancer patients and can improve quality of life and physical activity. However, the evidence for beneficial effects on body weight and fat-free mass remains inconsistent. Research should focus on early intervention and on multimodal treatment strategies, with attention to the adherence and feasibility of n-3 PUFA supplementation methods.

**Acknowledgements**

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**Abbreviations list**

ADA, American Dietetic Association; BMT, bone marrow transplant; EPA, eicosapentaenoic acid; GI, gastrointestinal; ONS, oral nutritional supplement; PIF, proteolysis-inducing factor; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; REE, resting energy expenditure; SGA, Subjective Global Assessment; TEE, total energy expenditure

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Systematic review