Omega-3 fatty acids in cancer

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Purpose of review
Significant achievements have been obtained in cancer treatment, but the clinical relevance of drug approach in daily practice remains questionable due to the high costs, limited efficacy, and negligible influence on quality of life. A new concept is emerging which is based on the early combination of chemotherapy and nutrition therapy.

Recent findings
Inflammation dictates tumour initiation, progression and growth. Omega-3 fatty acids exert anti-inflammatory effects, and therefore recent studies investigated their role in cancer prevention, in cancer cachexia treatment and in enhancement of antitumour therapies. Limited evidence suggests a role for omega-3 fatty acid supplementation in cancer prevention, but they have been shown to preserve muscle mass and function in cancer patients even during active treatment. During chemotherapy, omega-3 fatty acids may contribute to a reduced inflammatory response, but whether cancer treatment toxicity can be prevented remains to be assessed. Finally, small studies showed that omega-3 fatty acids increase response rate to chemotherapy.

Summary
Combination of chemotherapy and omega-3 supplementation appears an effective strategy to enhance the clinical outcome of cancer patients in their curative and palliative clinical trajectory.

Keywords
cachexia, DHA, EPA, response rate, toxicity

INTRODUCTION

During the past decade, better understanding of the mechanisms of carcinogenesis, cancer progression and resistance to treatment has been achieved. Therefore, it is not surprising that the incidence rates of many cancers and the relative risk of cancer death are both declining [1]. Nevertheless, the current drug approach to cancer is disappointing since it delivers statistically significant results, whose clinical relevance is questionable due to high costs, suboptimal response rate, increased toxicity and negligible impact on quality of life [2▪▪,3]. It is therefore becoming imperative to integrate traditional therapies with new concepts, which may enhance their efficacy, ideally at a fraction of the financial costs currently needed.

A promising concept is combination of drugs targeting cancer cells with strategies supporting the host or priming his/her metabolism. Indeed, in daily clinical practice cancer cells do not exist *per se*, rather patients with cancer. Therefore, any effective therapeutic strategy should target the cancer while simultaneously supporting the host [4]. Preliminary observations showed that integrating supportive care, that is, psychological support, nutritional care and pain control, during active treatment in lung cancer patients resulted in reduced distress and enhanced survival [5]. It is therefore tempting to speculate that specific nutrients given at specific doses and at critical time points in the clinical journey of cancer patients may increase response rate to treatment and improve patient centred outcomes.

OMEGA-3 FATTY ACIDS AND CANCER PREVENTION

Among the many nutrients with metabolic effects potentially relevant to cancer patients, polyunsaturated omega-3 fatty acids received intense attention

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KEY POINTS

- The clinical relevance of the current drug approach to cancer patients is at least questionable.
- Early integration of supportive care into active treatment increases survival and reduces psychological distress of cancer patients.
- Omega-3 fatty acids are metabolically active lipids with anti-inflammatory properties.
- Omega-3 fatty acids may reverse cancer cachexia, improve muscle mass and lean body mass, and promote weight maintenance.
- Considering the role of inflammation in tumour metabolism and in drug resistance, there is a strong rationale for their use in combination with anticancer therapies.
- Although limited evidence exists regarding the role of omega-3 fatty acids in preventing tumour development, their use in cancer patients has been demonstrated in small studies to improve nutritional status and function, to possibly reduce cancer treatment toxicity and increase response rate.

by clinicians and epidemiologists since the late 1980s. Omega-3 fatty acids are mainly derived from fish oil, and are characterized by the presence of a double bond on the third carbon atom from the methyl end of the carbon chain (omega end). The omega-3 fatty acids with clinically relevant effects in the oncology setting are eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and α-linolenic acid (ALA), due to their anti-inflammatory effects.

Omega-3 fatty acids, and in particular EPA, are metabolized by the same enzymes, that is, lipoxygenase and cyclooxygenase, which metabolize polyunsaturated omega-6 fatty acids, including arachidonic acid. However, the mediators of inflammation, that is, thromboxanes and prostaglandins, deriving from arachidonic acid, exert greater inflammatory activity when compared with the mediators deriving from EPA. Therefore, a diet rich in EPA would negatively modulate the inflammatory cascade [6▪▪]. Considering the impact of inflammation on the initiation and progression of cancer cells [7], a diet rich in omega-3 fatty acids may protect from cancer, at least at certain sites [8▪].

Gerber [9▪] has recently reviewed prospective and case-control observational studies investigating the possible protective effects of the dietary intake of omega-3 fatty acids on cancer development. Available evidence seems to suggest that ALA *per se* is neither a risk factor nor a beneficial factor for cancers. Interestingly, only observational studies on colorectal, prostate and breast cancers showed limited evidence on the possible role of omega-3 fatty acids in cancer prevention because insufficient homogeneity of the observations [9▪]. Indeed, epidemiological studies suffer from heterogeneity due to inherent difficulties (i.e. confounding and dietary pattern context, measurement error, level of intake, genetic polymorphisms); nevertheless it appears that cancer prevention cannot be attributed to a single nutrient, but other factors, including genetic background and lifestyle, play an important role as well. This may explain why intervention studies involving single nutrients frequently failed to prevent chronic diseases [10].

OMEGA-3 FATTY ACIDS AND CANCER CACHEXIA

Progressive and irreversible deterioration of nutritional status, that is, cachexia, is a frequent complication of tumour growth. Unlike starvation-induced malnutrition, cancer cachexia is not reversed by standard nutritional support since cachexia results from the combination of anorexia, reduced food intake and profound metabolic changes which are responsible for the onset of anabolic resistance [11▪▪]. The main characteristic of cancer cachexia is the progressive loss of muscle mass [11▪▪] leading to sarcopenia, which in turn translates into clinically relevant negative consequences. Lieffers *et al.* [12▪] have recently observed in 234 colorectal cancer patients undergoing surgery that the prevalence of sarcopenia is approximately 38%. More importantly, infection risk was greater (23.7 vs. 12.5%) and length of hospital stay was longer (15.9 vs. 12.3 days) for sarcopenic patients overall, especially for those older than 65 years [12▪]. In a multivariate model in patients older than 65 years, sarcopenia was an independent predictor of both infection and rehabilitation care [12▪]. Similarly, Parsons *et al.* [13▪] showed in advanced cancer patients that the majority of them are overweight and sarcopenic. Interestingly, sarcopenia reduced expected survival, irrespectively of patients' BMI [13▪]. Finally, Prado *et al.* [14] showed in patients with solid tumours that the presence of sarcopenic obesity was associated with poorer functional status compared with obese patients who did not have sarcopenia, and independently predicted survival.

Inflammatory cytokines play a significant role in the pathogenesis of cancer cachexia [15]. Consequently, the anti-inflammatory effects of omega-3 fatty acids may be of benefit in the prevention and treatment of cancer cachexia. Ries *et al.* [16▪] systematically reviewed 38 papers testing this hypothesis. In general, smaller trials reported a good effect of

omega-3 fatty acids in patients with advanced cancer and cachexia [16▪]. However, larger randomized controlled trials could not support the positive results, as they mostly did not find a significant effect [16▪]. Similar conclusions were reported by van der Meij *et al.* [17▪▪] who systematically reviewed omega-3 fatty acid trials in cancer patients. Some benefits were found for oral supplementation of omega-3 fatty acids on body weight (but not on lean body mass) and quality of life in cancer patients during chemo-radiotherapy and in palliative care [17▪▪]. Effects on Karnofsky Performance Status and survival were inconsistent [17▪▪].

Available data are insufficient to draw any robust recommendation for the use of omega-3 fatty in the prevention/treatment of cancer cachexia since available clinical studies are highly heterogeneous (Table 1). Also, the number of cancer patients involved in these trials is generally limited, making it difficult to generalize the results obtained to the whole oncologic population. Therefore, the many confounding elements still permeating this research field may contribute to the lack of robust evidence. Indeed, when well designed although small clinical trials are considered (i.e. homogeneous patients not yet in the refractory phase of cachexia, stratified in active and control groups, supplemented with enough dose of omega-3 fatty acids on top of energy and protein requirements), then the results appear promising [18▪]. Indeed, van der Meij *et al.* have recently studied 40 lung cancer patients receiving multimodality treatment [19▪]. Patients were then stratified to receive an EPA-enriched oral nutritional supplement ($n = 20$) or an isocaloric standard supplement for 5 weeks. Results show that EPA-supplemented patients improved quality of life and functional status when compared to the control group [19▪]. Similar results were obtained by Murphy *et al.* [20▪] who studied 40 lung cancer patients receiving active treatment. Patients were invited to take fish oil supplementation (i.e. 2.5 g EPA + DHA/day) during chemotherapy. After approximately 10 weeks, patients in the control group ($n = 24$) experienced an average weight loss of 2.3 kg, whereas patients receiving fish oil maintained their weight [20▪]. Patients with the greatest increase in plasma EPA concentration after fish oil supplementation were found to have the greatest gains in muscle [20▪]. Approximately 69% of patients in the fish oil group gained or maintained muscle mass. Comparatively, only 29% of patients in the control group maintained muscle mass, and overall the control group lost 1 kg of muscle [20▪]. Weed *et al.* [21] investigated in 31 head and neck cancer patients the effects of the perioperative supplementation of an EPA-enriched oral nutritional supplement on lean body mass. The results obtained show that this perioperative nutritional intervention, started not later than 2 weeks prior to surgery, was associated with a 3.2 kg gain in lean body mass [21]. Although interesting, the clinical relevance of this study is limited by the lack

Table 1. Factors determining heterogeneity of clinical trials testing the effect of omega-3 fatty acids on cancer cachexia

Factor	Variables
Type of supplement	Fish oil
	Omega-3 fatty acids
	EPA
Dose	1 g/day
	2 g/day
	2.5 g/day
	3 g/day
Clinical setting	Curative phase/palliative phase
	Advanced disease/early disease
Outcome measure (i.e., definition of cachexia)	Weight loss
	Sarcopenia
	Lean body mass
	Physical function
Nutritional support/composition of the supplement	EPA enriched oral nutritional supplements (liquid)
	EPA containing sachets (powder)
	EPA containing capsules
	Fish oil containing capsules

of a control group. It is therefore mandatory that a more global consensus is reached among researchers on key standards to be used in clinical trials on cancer cachexia.

OMEGA-3 FATTY ACIDS AND CANCER TREATMENT TOXICITY

The development of haematological, gastrointestinal or dermatological toxicities during or soon after completion of anticancer therapies compromises the delivery of adequate treatment to cancer patients and jeopardizes their chances to obtain clinical benefits [22▪]. Consistent evidence demonstrate that dose-limiting toxicity in cancer patients is related to sarcopenia [23,24▪]. Considering the role of omega-3 fatty acids in preserving/restoring muscle mass in cancer patients, it could be hypothesized that fish oil supplementation may reduce chemotherapy associated toxicity by improving lean body mass.

Murphy *et al.* [25▪▪] studied 46 lung cancer patients receiving first-line chemotherapy, who were invited to consume 2.5 g EPA+DHA/day. After approximately 10 weeks of supplementation, no difference in the incidence of dose-limiting toxicity was observed between patients receiving fish oil ($n=15$) and nonsupplemented patients ($n=31$) [25▪▪]. A finding of note was that supplemented patients significantly increased their muscle mass when compared to controls [20▪]. Machon *et al.* [26] orally supplemented 31 head and neck cancer patients for 5 days before each cycle of chemotherapy with an enriched formula, containing 3 g EPA+DHA/day, immune enhancing amino acids and a mix of antioxidant vitamins and micronutrients. At baseline, levels of inflammatory, pro-angiogenic and pro-oxidative stress markers were increased, but inflammatory markers significantly decreased after supplementation [26]. After 6 weeks of radiochemotherapy, 19 of the 31 eligible patients experienced at least an NCI grade 3 or 4 acute toxicity, including five patients (16%) with grade 3 or 4 mucositis. The clinical relevance of this study is limited by the lack of a control group. However, the authors highlight that in their study the incidence of severe acute mucositis was 16 vs. 45% in the available and comparable literature [26].

Although published studies are inconclusive due to the small populations involved and the lack of control groups, nevertheless the robustness of observational studies seems to suggest a causative inverse link between muscle mass and cancer treatment toxicity. Therefore, the role of muscle mass in preventing chemotherapy-induced toxicity should be further investigated, and factors associated to muscle mass, that is, physical exercise or drug pharmacokinetics, should also be considered.

Neutropenia and impaired neutrophil function are frequent toxic effects of cancer chemotherapy and lead to dose reduction when severe. Bonatto *et al.* [27▪] recently tested whether omega-3 fatty acids supplementation improved neutrophil function in cancer patients receiving chemotherapy. Results show that nonsupplemented cancer patients receiving 5-fluorouracil and leucoverin lost 2.5 kg of weight over the 8 weeks of the study. Also, the number of blood polymorphonuclear cells, mainly neutrophils, and their functions (phagocytosis and hydrogen peroxide production) significantly decreased. In contrast, daily supplementation of 0.3 g EPA and 0.4 g DHA prevented these decreases and actually increased body weight, polymorphonuclear cell number, phagocytosis and superoxide production. These results are encouraging but more trials are needed to assess whether the protective effects of EPA and DHA on neutrophil number and function translate into clinically relevant outcomes (i.e. prevention of infections, reduction of treatment interruptions due to neutropenia).

OMEGA-3 FATTY ACIDS AND RESPONSE TO TREATMENT

The tumour inflammatory microenvironment plays a major role in growth, invasiveness and resistance to therapy [28]. On the contrary, food is a potent inducer of metabolic responses. Therefore, modulation of food intake may impact on tumour growth, by sensitizing cancer cells to chemotherapy and increasing resistance of normal cells to the toxic effects. In animal models, this hypothesis has been tested by using extreme nutritional stress. Lee *et al.* [29▪▪] studied the effects of short term fasting on cultured cancer cells and in animal models. Results obtained showed that multiple cycles of fasting promote differential stress sensitization in a wide range of tumours and could potentially replace or augment the efficacy of certain chemotherapy drugs in the treatment of various cancers [29▪▪]. However, translation of this approach in clinical practice could be difficult and not advisable since cancer patients are already prone to the development of malnutrition and cycles of fasting may accelerate the onset of cachexia [30▪]. Since tumour growth appears to be related to the circulating levels of glucose and insulin-like growth factor I (IGF-I) [29▪▪], any nutritional intervention inhibiting the IGF-I axis may also lead to increased sensitization of cancer cells to chemotherapy and increased resistance of normal cells to cancer treatment toxicity. Interestingly, experimental evidence showed that

plasma IGF-I decreased with increasing dietary omega-3 : omega-6 ratio [31]. Therefore, omega-3 fatty acid supplementation could represent a clinically relevant adjuvant therapy in cancer patients.

Recent evidence shows that omega-3 fatty acid supplementation increases cancer cell apoptosis. Benais-Pont *et al.* [32] demonstrated that preincubation with omega-3 fatty acids induced a dose-dependent additive decrease in colorectal cancer cell survival after irradiation. Evaluation of the underlying mechanisms indicated that omega-3 fatty acids mainly decreased the cell number via apoptosis induction [32]. Supporting this evidence, Fukui *et al.* [33] demonstrated that feeding animals with a diet supplemented with high levels of EPA and DHA inhibits the growth of human pancreatic cancer xenografts in athymic nude mice by inducing oxidative stress and cell death. However, EPA can concomitantly induce autophagy in cancer cells, and the induction of autophagy diminishes its ability to induce apoptotic cell death [33].

In cancer patients, promising results have been obtained. Bougnoux *et al.* [34] evaluated the safety and efficacy of the addition of 1.8 g DHA daily to an anthracycline-based chemotherapy regimen in 25 breast cancer patients with rapidly progressing visceral metastases. Results obtained showed that the objective response rate, time to progression and overall survival were within the ranges reported in the literature [34]. However, when patients are stratified according to high or low DHA incorporation into cell membranes, survival is almost doubled in high incorporating vs. low incorporating patients (34 and 18 months, respectively) and longer than the average overall survival reported in the literature, that is, 18–23 months [34]. It is likely that tumour cells were made more sensitive to chemotherapy when membrane lipids were enriched with DHA, an oxidative stress-inducing lipid [34]. More recently, Murphy *et al.* [25▪▪] studied 46 lung cancer patients receiving first-line chemotherapy. Patients were invited to take fish oil (2.5 g EPA + DHA/day) during chemotherapy cycles, as tablets or liquid product. At the end of the study, patients supplemented with fish oil ($n = 15$) had an increased response rate (60.0 vs. 25.8%) and greater clinical benefit (80.0 vs. 41.9%) when compared to those observed in the standard of care group. Surprisingly, the incidence of dose-limiting toxicity did not differ between groups although fish oil supplemented patients increased their muscle mass [20▪,25▪▪]. Also, 1-year survival tended to be greater in the fish oil group (60.0 vs. 38.7%; $P = 0.15$) [25▪▪].

When considered together, this evidence suggests that omega-3 fatty acids may exert a direct inhibitory effect on cancer cells *in vivo* (proapoptotic effect?), beyond their potential for reducing cancer treatment toxicity. Considering the cost of omega-3 fatty acid supplementation when compared to chemotherapy, even achieving a 30% increase in response rate by integrating EPA/DHA in standard treatment of cancer patients would prove to be highly cost-effective.

CONCLUSION

Integration of omega-3 fatty acid supplementation into the therapeutic approach to cancer patients is a novel and promising concept, which goes beyond their potential role in reversing cancer cachexia, promoting weight maintenance and improving muscle mass. Preliminary observations suggest that statistically significant and clinically relevant achievements could be obtained in terms of enhanced efficacy of anticancer drugs, reduced toxicity and enhanced quality of life. The next frontier is including nutrition therapy into clinical trials testing the efficacy of chemical entities in cancer patients: in this way, by testing this combination in a large population, a definitive answer to the therapeutic role of omega-3 fatty acids will be achieved and general recommendations could be issued. Evidence in this area is being constantly produced, which strongly suggests the general tenet of clinical nutrition, that is, 'never underestimate the power of food'.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

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▪ of special interest
▪▪ of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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