The impact of n-3 polyunsaturated fatty acids in patients with cancer : emerging themes

Current Opinion in Clinical Nutrition and Metabolic Care

van der Meij, Barbara; Parsons, Sarah; Mazurak, Vera

https://doi.org/10.1097/MCO.0000000000001102

The impact of n-3 polyunsaturated fatty acids in patients with cancer: emerging themes

Barbara van der Meij[a,b], Sarah Parsons[c] and Vera Mazurak[c]

Purpose of review

This review summarizes recent literature falling broadly under the topic of n-3 polyunsaturated fatty acids (PUFAs) in the oncology setting, highlighting emerging themes and emphasizing novel explorations.

Recent findings

Meta-analyses continue to confirm safety and efficacy of n-3 PUFA supplementation on reducing inflammation and improving survival in people with cancer. Common themes in recent studies emphasize improving tumor-directed efficacy and reducing toxicities of common cancer therapies. New areas of interest include the impact of n-3 PUFA when combined with immunotherapies and applications in pediatric acute lymphoid leukemia. Novel assessments include specialized pro-resolving lipid mediators, the intestinal microbiome and psychological well being. A variety of clinically relevant outcomes including nutritional status, toxicities and survival are being explored in ongoing clinical studies.

Summary

Evidence confirms the safety of n-3 PUFA for patients with cancers, as well as benefits in some, but not all areas of exploration. Larger, well designed trials with biological assessment of compliance compared to the prescribed n-3 PUFA dose would strengthen the evidence needed to integrate n-3 PUFA recommendations into clinical practice for patients with cancer.

Keywords

chemotherapy, clinical trial, docosahexaenoic acid, eicosapentaenoic acid, fish oil, polyunsaturated fatty acids, toxicities

INTRODUCTION

A wealth of literature exists on the impact of long-chain n-3 polyunsaturated fatty acids (PUFAs) in the oncology setting. α-Linolenic acid is a dietary essential n-3 fatty acid found in plant oils. The longer, more polyunsaturated n-3 fatty acids, eicosapentaenoic acid (EPA) and docosohexaenoic acid (DHA), are found in the oils of fatty fish, seafood, and algae and exhibit greater biological activity than linolenic acid. Themes involving n-3 PUFAs and cancer that have dominated the cancer literature in the last 25 years span cachexia, muscle wasting, side effects of cancer treatment, quality of life and survival. Long-chain n-3 PUFAs have well established effects on the immune system [1,2] and muscle condition [3] in the context of chronic disease. However, evidence for the impact on patients with cancer in clinical studies is conflicting and n-3 PUFAs in the oncology setting are not consistently part of clinical practice guidelines. The purpose of this review is to summarize current trends in the recent literature, highlighting emerging themes with an emphasis on novel explorations in relation to the impact of n-3 PUFAs in cancer. Strategically designed research studies will improve the evidence available for making n-3 PUFA recommendations that benefit patients with cancers.

APPROACH

A literature search identified published meta-analyses and clinical studies in the past 18 months on the topic of ‘n-3 PUFAs and the cancer patient’. Registered protocols reported on clinicaltrials.gov that do not yet have published results were also explored to highlight emerging themes.

[a]Department of Human Nutrition and Health, Wageningen University & Research, [b]Nutrition, Dietetics and Lifestyle, HAN University of Applied Sciences, Nijmegen, the Netherlands and [c]Division of Human Nutrition, Department of Agricultural, Food and Nutritional Science. University of Alberta, Edmonton, Alberta, Canada

Correspondence to Vera Mazurak, Department of Agricultural, Food and Nutritional Science. University of Alberta, Edmonton, AB, Canada T6G 2P5. E-mail: vmazurak@ualberta.ca

Curr Opin Clin Nutr Metab Care 2024, 28:000–000

DOI:10.1097/MCO.0000000000001102

KEY POINTS

- Evidence continues to grow for safety and efficacy for reducing inflammatory markers, reducing side effects and increasing survival with n-3 PUFAs in patients with cancer.
- New populations under study for n-3 PUFA interventions include participants with pediatric cancers and those undergoing immunotherapy.
- Novel measures include oxylipins and specialized pro-resolving mediators derived from n-3 PUFAs as well as modulation of the microbiome to enhance outcomes during active treatment.
- Biological measures of n-3 PUFA status must be applied to improve evidence around doses of n-3 PUFAs required in the clinical setting.

Thirty-three relevant publications were reviewed: 17 human studies, 10 experimental studies, and 6 meta-analyses. Fourteen ongoing studies were registered on clinicaltrials.gov.

Recent meta-analyses and systematic reviews

Relevant meta-analyses included studies with large sample sizes, consistently demonstrating the safety of n-3 PUFAs (conclusions presented in Table 1). No serious adverse events were identified with n-3 PUFA supplementation in patients with a variety of chronic diseases across 90 studies involving 55 940 participants [4]. Patients with cancer in the surgical setting who received n-3 PUFAs with or without (neo-)adjuvant chemotherapy experienced shorter length of stay and anti-inflammatory effects [6]. Evidence was mixed on the impact of n-3 PUFAs on nutritional status and quality of life across clinical settings from significant effects to no effects [6,9]. However, no meta-analysis to date has raised concern about safety with doses used in clinical studies (up to 5 g/day of n-3 PUFAs).

Clinical studies

Randomized controlled trials (RCTs) published in the past 18 months included a variety of outcome measurements and cancer types including breast

Table 1. Systematic reviews and meta-analysis

Reference	Title	Number of studies included and total number of participants (*n*)	Conclusion
Chang *et al.*, 2023 [4]	Safety of supplementation of omega-3 polyunsaturated fatty acids: a systematic review and meta-analysis of randomized controlled trials	90 studies; $n=55\,940$ mixed chronic disease (no cancer)	n-3 PUFA supplementation is safe
Guo *et al.*, 2023 [5]	n-3 PUFA can reduce IL-6 and TNF levels in patients with cancer	19 studies; $n=959$ (cancer)	n-PUFA ↓ circulating IL-6 and TNF-α levels
Lui *et al.*, 2023 [6]	Efficacy and safety of omega-3 polyunsaturated fatty acids in adjuvant treatments for colorectal cancer: a meta-analysis of randomized controlled trials	19 studies; $n=1556$ (colorectal cancer)	↓LOS ↓TNF-α and IL-6 No impact on CRP, IL-1β, albumin, BMI, weight, infectious and noninfectious complication rates or quality of life
Wang *et al.*, 2023 [7■■]	Dietary fish and omega-3 polyunsaturated fatty acids intake and cancer survival: a systematic review and meta-analysis	12 studies; $n=26\,518$ (cancer) for overall survival 11 studies; $n=24\,134$ (cancer) for cancer survival	Protective effect of dietary fish and marine n-3 PUFA consumption on cancer survival
Khosharahi *et al.*, 2024 [8]	The effects of omega-3 fatty acids supplementation on inflammatory factors in cancer patients: a systematic review and dose–response meta-analysis of randomized clinical trials	33 studies; $n=2068$ (cancer)	n-PUFA ↓ circulating IL-6 and TNF-α levels
Sasanfar *et al.*, 2024 [9]	Effects of n-3 polyunsaturated fatty acid supplementation on appetite: a systematic review and meta-analysis of controlled clinical trials	15 studies; $n=1504$ (healthy, obese, cancer, anxiety and Alzheimer)	n-3 PUFA have no effect on appetite scores n-3 PUFA increase the desire to eat

CRP, C-reactive protein; IL, interleukin; LOS, length of stay; PUFA, polyunsaturated fatty acids; TNF, tumor necrosis factor-alpha.

[10–13], lung [14–16], colorectal [17], prostate [18,19,20▪] and pancreatic/biliary cancers [21]; acute lymphoblastic leukemia [22,23] (one study, two publications); and mixed cancer types [24,25▪▪,26▪▪] (Table 2). Dose and duration of n-3 PUFA supplementation via capsules varied widely (Fig. 1) with one study providing n-3 PUFAs for oral application through a nanoemulgel [27]. One study provided a high-dose and low-dose n-3 PUFA diet via fatty fish [13] and another assessed adherence to the Mediterranean diet [28]. The majority of clinical studies evaluated the impact of n-3 PUFAs during active treatment of surgery [12,18,19], chemotherapy [10,11,13,14,22,23], radiotherapy or immunotherapy [15]. These studies confirmed the previously reported antiinflammation and survival benefits of n-3 PUFAs, but showed inconsistent results of n-3 PUFAs for pain, infection, complications, and quality-of-life measures. Inconsistent results among studies may be related to variations in dose, patient population and intervention length (Fig. 1). A biological measure of compliance (i.e. assessment of n-3 PUFAs in blood or other tissue) upon which to standardize outcome measures would enable an optimal dose for specific outcomes to be reconciled.

Fourteen additional clinical studies were registered on clinicaltrials.gov (Table 3). The majority of these ongoing studies are enrolling patients with active breast [29,30], esophageal [31], gastrointestinal [32–35], lung [36–38] or mixed [39] cancers. Three studies are enrolling survivors with prostate [40] or breast [41,42] cancer. Conventional outcomes such as nutritional status, treatment toxicities and quality of life are being assessed. Compared to prior literature, ongoing studies provide n-3 PUFAs in combination with other nutrients purported as anticancer and anti-inflammatory and are multimodal interventions including physiotherapy and counseling. Scaffolding n-3 PUFAs as part of a multimodal intervention may lead to enhanced standard of care in oncological practice. Nutritional intervention studies in cancer survivors fill a gap in the oncology literature that will inform dietary recommendations to restore post-therapy nutritional disruptions.

Large, population-based studies

The UK Biobank provides an additional tool for evaluating potential protective effects of n-3 PUFAs on cancer risk in a large number of participants without the need for costly long-term interventions. Three published studies in the last 18 months using the UK Biobank evaluated blood measures of EPA and DHA as biomarkers of fish (oil) intake. These three studies revealed a negative association of plasma n-3 PUFA levels with hepatocellular carcinoma [24] and cancer-related or all-cause and cause-specific mortality [16,25▪▪].

Experimental studies

Several preclinical *in-vitro* and *in-vivo* studies test whether provision of n-3 PUFAs provided with chemotherapy increase anticancer activity on specific tumor types or mitigate chemotherapy toxicities [20▪,43–51]. The combination of these outcomes is the ultimate goal of oncological therapy. Emerging in the preclinical literature are studies assessing the interactions between targeted therapies and n-3 PUFAs. A combination of immunotherapy and n-3 PUFAs enhanced tumor death in esophageal squamous cell carcinoma, Colon-26 (C26) carcinoma and human osteosarcoma cells. Mechanisms are linked to induction of ferroptosis, reactive oxygen species and immune cell infiltration into tumors. To enhance translatability of these approaches, attention to doses of EPA and DHA with the appropriate experimental controls must be considered. More clinical and experimental studies are expected in future that explore the synergistic effect of n-3 PUFAs and immunotherapy or other targeted therapies.

Emerging applications for n-3 polyunsaturated fatty acids in patients with cancer

Pediatric cancers

Studies of n-3 PUFAs in pediatric cancers are limited. Podpeskar *et al.* [52] summarized evidence for n-3 PUFA supplementation in pediatric cancers and found improvements in nutritional status and a reduction in toxicities from drugs commonly used to treat pediatric lymphocytic leukemia. Curative treatments for pediatric cancers cause long-term, late toxicities that result in a metabolic syndrome phenotype long after completion of cancer treatment. Therefore, studies focus on mitigating changes to body composition and metabolism. Children (3–13 years old) newly diagnosed with acute lymphoid leukemia [23] were allocated to daily n-3 PUFAs or a placebo (sunflower oil) supplement in addition to an oral nutritional supplement for the first 3 months of treatment. Children in the n-3 PUFA group experienced less loss of lean body mass compared to the placebo group. Compared to the placebo group, lower levels of triglycerides, VLDL-C, IL-6 and atherogenic index of plasma (AIP) were experienced by the n-3 PUFA group though they had a higher concentration of total cholesterol [22]. This study has been criticized for its small sample

Table 2. Human studies investigating the impact of n-3 polyunsaturated fatty acids on various outcomes in the oncology setting

Reference	Study type	Population	Sample size, age and sex (M:F)	Treatment	Primary outcome	Effect of n-3 PUFAs
Chemotherapy						
Arsic *et al.*, 2023 [10]	RCT	Postmenopausal breast cancer	n-3 PUFA: $n=14$ C: $n=15$	Anthracycline-based chemotherapy	Systemic inflammation (plasma cytokines) Anthropometrics	↓ IL-6 in both groups No difference in anthropometrics
Barbosa-Cortez *et al.*, 2023 [22]	RCT	Children with acute lymphoid leukemia	n-3 PUFA: $n=19$ (8 : 11) C: $n=22$ (10 : 12) Age; 3–13 years	Chemotherapy (HP09 Protocol)	Cardiometabolic factors (TG, inflammatory cytokines, HDL-C)	Small difference in IL-6 ↓ VLDL, TG, AIP ↓ Total cholesterol
Barbosa-Cortez *et al.*, 2023 [23]	RCT	Children with acute lymphoid leukemia	n-3 PUFA: $n=19$ (8 : 11) C: $n=22$ (10 : 12) Age; 3–13 years	Chemotherapy (HP09 Protocol)	Body composition	↓ Loss of lean body mass during first 3 months of treatment
Gui *et al.*, 2023 [14]	RCT	Lung cancer	n-3 PUFA: $n=18:12$ C: $n=33$ (20 : 13), age = 62 years	Cisplatin singlet or doublet chemotherapy	Nutritional status (NRS-2002, anthropometrics) and inflammation (CRP, TNF, IL-6, IL-8, IL-1, IFN-γ)	↑ Albumin and hemoglobin ↓ CRP, IL-1, IL-6, IL-8, TNF-α
Tawfik *et al.*, 2023 [11]	RCT	Breast cancer	n-3 PUFA: $n=25$, C: $n=24$ (m : f) Mean age = 53 years	Paclitaxel	Peripheral neuropathy Paclitaxel-associated acute pain syndrome	No effect
Xu *et al.*, 2023 [13]	RCT	Breast cancer survivors	Diet intervention: high fish: $n=20$: low fish: $n=13$	6–24 months after treatment for stage 1–IIA breast cancer	Feasibility; psychoneurological symptoms (pain, depression, fatigue, sleep, stress)	↓ Depression ↓ Fatigue ↓ Stress ↑ Sleep Feasibility was demonstrated
LaChance *et al.*, 2024 [20▪]	RCT	Prostate cancer	EPA: $n=21$ C: $n=21$	Preprostatectomy	Tumor progression	Reduced cancer upgrading ↓ Fecal Ruminococcaceae and butyrate levels
Surgery						
Khalenberg *et al.*, 2023 [12]	RCT	Estrogen receptor-positive breast cancer with obesity	n-3 PUFA: $n=25$ C: $n=6$	Surgery	Surgical site healing complications and infections	No difference between groups
Moussa *et al.*, 2023 [18]	RCT	Prostate cancer	EPA: $n=65$ C: $n=65$ Age 62.5 ± 7.36 years	Presurgery	Quality of life (IPSS; EPIC-26)	↑ Urinary function at 12 months
Savard *et al.*, 2023 [19]	RCT	Prostate cancer	EPA: $n=65$ C: $n=65$ Age 62.5 ± 7.36 years	Presurgery	Quality of life (depression, PHQ, FCRI-S, FSI, ISI, FACT- Cog v3)	No impact

Table 2 (*Continued*)

Reference	Study type	Population	Sample size, age and sex (M:F)	Treatment	Primary outcome	Effect of n-3 PUFAs
Observational						
Abe *et al.*, 2024 [21]	OBS	Pancreatic and biliary cancer	*n* = 45 (28 : 17) Age 37–83 years	Mixed (FOLFIRINOX or gemcitabine/ cisplatin based)	Sarcopenia Overall survival	Low EPA levels more prevalent in those with sarcopenia and shorter survival
Fuller *et al.*, 2023 [17]	OBS	Participants in the English Bowel Cancer Screening Programme at high risk for colon cancer	'High-risk' colorectal polyp findings: *n* = 400 (325 : 75), age 55–73 years	Subset from a prior intervention study	Oxylipin production	↑ 18-HETE and 15-HEPE in plasma and rectal mucosa No effect on SPM, resolvin E1 or 15-epi-LXA4.
Lui *et al.*, 2024 [24]	OBS	Hepatocellular carcinoma	UK biobank, *n* = 252 398	Population-based	Incident HCC	↓ Association between plasma n-6 and n-3 PUFAs and risk of incident HCC
O'Keefe *et al.*, 2024 [25■■]	OBS	UK Biobank participants	UK Biobank + results from FORCE: *n* = 160 404 individuals and 24 342 deaths during a median of 14 years of follow-up	Population-based	Survival	Higher DHA levels were associated with ↓ in all-cause mortality ↓ Risk of deaths due to CV disease, cancer, and all other causes
Tanaka *et al.*, 2024 [15]	OBS	Lung cancer	Short-term survivors (<3 years) (10 : 2) Long-term survivors (≥3 years) (6 : 2); 70–82 years	Pembrolixumab	Survival	↑ Survival in patients with higher EPA and DHA in plasma
Zhang *et al.*, 2024 [16]	RSP	Lung cancer (stage 1–3)	n-3 PUFA: *n* = 52 C: *n* = 51 (24 : 27) (26 : 26) Age 58.4 ± 6.2 years	Not stated	Quality of life and symptoms (EORTC-QLQ-C30; PHQ-9)	↓ Insomnia, constipation ↑Physical and emotional function
Zhang *et al.*, 2024 [26■■]	OBS	UK biobank participants	UK Biobank *n* = 85 425 individuals Age 40–69 years	Population-based	Survival	n-3 PUFA levels associated with ↓ in all-cause mortality, CV disease and cancer-related deaths

DHA, docosahexaenoic acid; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EPA, eicosapentaenoic acid; EPIC, Expanded Prostate Cancer Index; FACT – Cog, Functional Assessment of Cancer Therapy – Cognitive Function; FCRI-S, Fear of Cancer Recurrence Inventory- Severity Subscale; FSI, Fatigue Symptoms Inventory; HCC, hepatocellular carcinoma; IL, interleukin; IPSS, International Prostate Symptom Score; ISI, Insomnia Symptoms Inventory; OBS, observational; PHQ, Patient Health Questionnaire; PUFAs, polyunsaturated fatty acids; RCT, randomized controlled trial; RSP, retrospective.

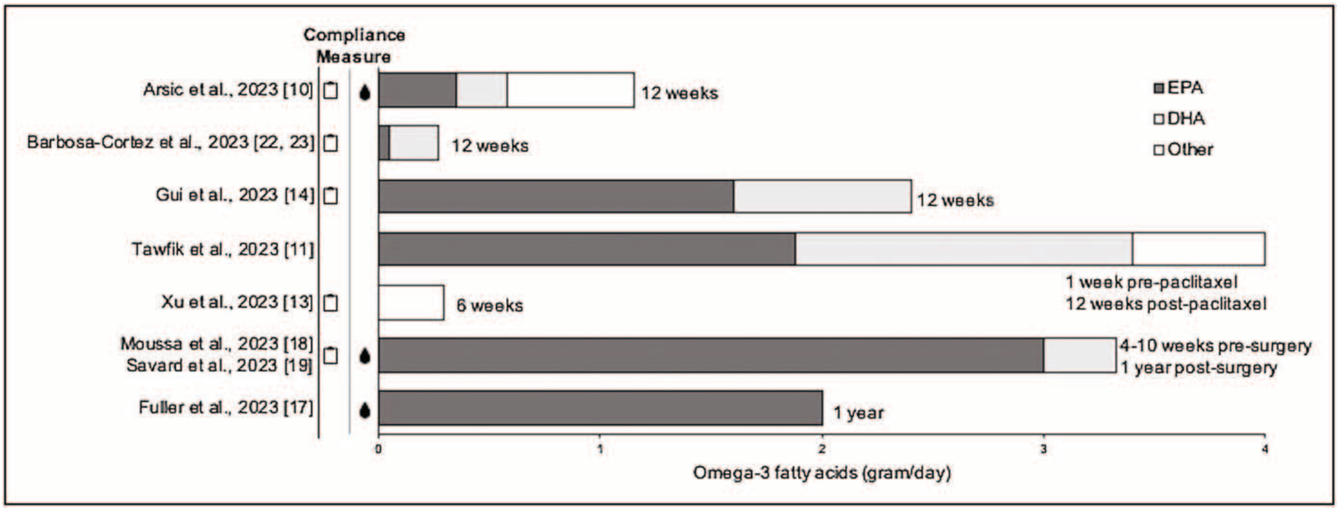

FIGURE 1. Depiction of the n-3 polyunsaturated fatty acid mixture provided as supplements in clinical studies as well as the duration and the measure of compliance expressed as a self-report ( ) or biological measure ( ). Moussa *et al.*, 2023 [18] and Savard *et al.*, 2023 [19] are secondary analysis studies of the same phase II double-blind placebo-controlled randomized trial but report omega-3 fatty acids differently. Data in this figure reflect the original study protocol referenced in Moussa *et al.*, 2023 [18] and Savard *et al.*, 2023 [19].

size and relatively short duration (3 months) [53], as well as for the potential confounding effects on lean body mass by physical activity and medications (anti-inflammatory and antineoplastic) [54]. Replication of these promising findings is warranted in large-scale RCTs in pediatric cancers to determine safety and efficacy of n-3 PUFAs and potential interactions with cancer therapy in children.

Enhancing efficacy of immunotherapies and targeted therapies

Immunotherapies and targeted therapies have emerged as first-line treatment in specific cancer types. One observational study in the past 18 months assessed the impact of n-3 PUFAs in this context [15]. In patients with nonsmall cell lung cancer, undergoing initial pembrolizumab treatment, researchers assessed the plasma EPA/arachidonic acid ratio as a marker of inflammatory state, as diets high in n-6 PUFAs and low in n-3 PUFAs can lead to a lower EPA/arachidonic acid ratio, indicative of a pro-inflammatory state. Patients who survived more than 3 years after treatment had higher serum EPA levels than patients who survived less than 3 years. Larger, prospective studies would confirm whether higher dietary intakes of n-3 PUFA and a higher EPA/AA ratio improve overall survival in patients with lung cancer treated with pembrolizumab. Two registered protocols are evaluating immunotherapy or targeted therapies in combination with n-3 PUFAs (Table 3) to assess impact on muscle mass [36], response rates, quality of life and survival [38].

Modification of oxylipins by n-3 polyunsaturated fatty acid

Oxylipins are bioactive lipid mediators derived from PUFAs by enzymatic and nonenzymatic reactions. Past studies have focused on inhibiting cyclooxygenase (COX)-2 or lipoxygenase enzymes to reduce arachidonic acid metabolites that are linked to proinflammatory-related effects on tumor progression. In the recent decade, specialized pro-resolving lipid mediators (SPMs) derived from EPA and DHA and, to a lesser extent, arachidonic acid, have garnered attention because they actively resolve inflammation, repair tissue, and clear immune cells and cellular debris. Fuller *et al.* [17] used biological samples from the Seafood Trial biobank [55] to explore whether SPMs or upstream oxylipin precursors were associated with patients receiving 2 g EPA alone and in combination with aspirin (300 mg) for 12 months. Levels of plasma and rectal 18-hydroxyeicosapentaenoic (18-HEPE), an EPA metabolite, and 15-hydroxyeicosatetraenoic acid (HETE), an arachidonic acid metabolite of acetylated COX-2, were higher in participants receiving oral EPA with or without aspirin. However, resolvin E1 and 15-epi-lipoxin A_4, SPMs derived from EPA and arachidonic acid, respectively, were below levels of detection, showing that the chemopreventative activity of EPA and aspirin is independent of SPMs. Additionally, 18-HEPE could not predict total colorectal polyp number in participants receiving EPA alone.

The recent Expert Consensus Report on Lipid Mediators [56] highlights SPMs as a potential factor through which EPA and DHA may preserve skeletal

Table 3. Studies investigating n-3 polyunsaturated fatty acids in patients with cancer, registered on clinicaltrials.gov

NCT number	Study type	Population	Sample size	Treatment	Dose of EPA and DHA	Duration	Primary outcome	Study status
NCT05331807 [29]	Open-label RCT	Breast cancer	*n* = 88 (actual)	Chemotherapy (Adriamycin + Cytoxan)	1) n-3 PUFA (360 mg EPA + 240 mg DHA) 2) Vitamin D (50 000 IU/week) 3) n-3 PUFA + vitamin D 4) No intervention	2 months	Nutritional status (body weight, muscle mass, PG-SGA), quality of life, TNF-α, CRP	Completed in May 2024, not published yet
NCT02538484 [30]	Open-label RCT	Breast cancer	*n* = 24 (actual) *n* = 60 (original)	Letrozole (aromatase inhibitor)	1) Fish oil 2.7 g/day[a] 2) Letrozole 2.5 mg/day 3) Fish oil + Letrozole	30 days	Aromatase target gene, aromatase level, PGE2	Completed in 2020, not published yet
NCT06392971 [31]	Quadruple-blinded RCT	Esophageal cancer	*n* = 120 (estimated)	Radiotherapy	1) Fish oil 2 g/day[a] 2) Placebo capsules 1 g/day	2 months	Acute radiation oesophagitis	Recruiting
NCT05253716 [32]	Open-label RCT	Gastric cancer	*n* = 696 (estimated)	Total gastrectomy	1) ONS + fish oil capsules 3/day[a] 2) Nutritional counselling)	6 months	3-year disease-free survival	Recruiting
NCT06047158 [33]	Prospective cohort study	Gastric cancer	*n* = 200 (estimated)	Radical surgery combined with HIPEC	1) n-3 PUFA emulsion 100 ml/day IV[a] 2) Placebo: no n-3 PUFA IV	5 days	Immune function (peripheral blood lymphocyte count, CRP, albumin, postoperative infectious complications)	Recruiting
NCT04699760 [34]	Single-blinded RCT	Colorectal cancer	*n* = 50 (actual)	Chemotherapy	1) ONS + EPA 2.2 g/day) 2) ONS	8 weeks	Nutritional status (body weight)	Completed in September 2015, not published yet
NCT05404230 [35]	Triple-blinded RCT	Colon or rectal cancer	*n* = 120 (estimated)	Adjuvant treatment with capecitabine ±oxaliplatin	1) n-3 PUFA (EPA + DHA 3 g/day) 2) n-6 PUFA (corn oil 2 g/day)	8 months	Chemotherapy-induced peripheral neuropathy	Recruiting
NCT04965129 [36]	Quadruple-blinded RCT	Nonsmall cell lung cancer	*n* = 50 (estimated)	Immunotherapy, chemotherapy and tyrosine kinase inhibitors	1) n-3 PUFA: EPA 2100 mg/day + DHA 924 mg/day 2) Olive oil	4 months	Muscle mass	Recruiting
NCT05955248 [37]	Quadruple-blinded RCT	Nonsmall cell lung cancer	*n* = 168 (estimated)	Surgery	1) ONS + 2.1 g EPA+1.32 g DHA 2) ONS + 2.1 g EPA+1.32 g DHA + structured exercise + home-based exercise 3) Placebo supplement	10 weeks (4 weeks prior to surgery, 6 weeks postsurgery)	Walking capacity (6MWT)	Recruiting

Table 3 (*Continued*)

NCT number	Study type	Population	Sample size	Treatment	Dose of EPA and DHA	Duration	Primary outcome	Study status
NCT06356701 [38]	Open-label phase I	Nonsmall cell lung cancer)	*n* = 120 (estimated)	Immune checkpoint inhibitors + chemotherapy	Supplements: fish oil[a] + bioactive ingredients[b]	1 year	Progression-free survival, overall response rate, quality of life	Recruiting
NCT02294149 [39]	Triple-blinded RCT	Any cancer	*n* = 600 (estimated)	Chemotherapy (platinum and/or taxane)	1) n-3 PUFA[a] and vitamin D_3, twice daily 2) Placebo supplement	6 months	Total neuropathy score	Completed November 2016, presented at ASCO 2015
NCT03753334 [40]	Quadruple-blinded RCT	Prostate cancer reoccurrence	*n* = 39 (actual)	Not specified	1) EPA 5 g/day, 2) Sunflower oil 5 g/day	12 months	PSA doubling time	Active, not recruiting
NCT06214598 [41]	Triple-blinded RCT	Breast cancer survivors	*n* = 90 (estimated)	Aromatase inhibitors	1) Anti-inflammatory diet 2) Fish oil (600 mg EPA+ 400 mg DHA+ 351 mg GLA) 3) Placebo capsules	4 months	Nutritional status (blood cell count, BMI, body composition) quality of life; clinical outcome (complications, side effects)	Recruiting
NCT02295059 [42]	Quadruple-blinded RCT	Breast cancer survivors	*n* = 80 (estimated)	Completion of surgery, radiation therapy and/or chemotherapy.	1) High dose n-3 PUFA (EPA + DHA 5.4 g/day) 2) Low-dose n-3 PUFA (EPA + DHA 0.9 g/day)	Up to 12 months	Eicosanoids/ metabolites (PGE_2, PGE_3) in breast adipose tissue	Active, not recruiting

ASCO, American Society of Clinical Oncology; CRP, C-reactive protein; ERAS, enhanced recovery after surgery; GLA, gamma-linolenic acid; HIPEC, hyperthermic intra peritoneal chemo infusion; IV, intravenous; MWT, meter walking test; NRS, Nutrition Risk Screening; NSCLC, nonsmall cell lung cancer; PG, prostaglandin; PG-SGA, patient-generated subjective global assessment; PSA, prostate-specific antigen; PUFA, n-3 polyunsaturated fatty acids; RCT, randomized control trial.
[a]Dose of EPA and DHA not specified.
[b]Anti-inflammatory diet: rich in whole grains fiber, vegetables, polyphenol-rich fruits, n-3 PUFA-rich foods.
[3]Bioactive agents: Spirulina Bifidobacterium, Grape Seed, Blueberry, Ganoderma Spore Oil.

muscle mass, a known prognostic factor in patients with cancers. The panel supports intravenous lipid emulsions that include EPA and DHA in clinical settings, to expedite delivery to plasma membrane phospholipid and peripheral tissues for potential biosynthesis of SPMs.

Targeting the intestinal microbiome

Modulation of the intestinal microbiome with n-3 PUFAs and related bacterial metabolites is well explored in intestinal cancer but not in cancers distant from the intestine. In a study that combined clinical and experimental approaches, researchers elegantly demonstrated that fecal microbiota transplants from patients with prostate cancer induced prostate cancer growth in mice [20▪]. In the same publication, supplementation with 3 g/day monoglyceride EPA in prostate cancer patients awaiting a prostatectomy was associated with reduced cancer upgrading, decreased fecal Ruminococcaceae, a major butyrate producer, and decreased fecal butyrate. Mice supplemented with EPA also had reduced prostate growth and decreased fecal Ruminococcaceae. These results indicate a potential suppression of cancer growth by n-3 PUFAs through modification of the intestinal microbiota and resulting metabolites.

Psychological and quality-of-life assessments

Quality of life is generally evaluated as a secondary outcome and often includes a single or, at most, a few basic questions on psychological well being. Given the anxiety that a cancer diagnosis and its treatment evokes, and that n-3 PUFAs are important components of the central nervous system and brain, n-3 PUFAs are of interest to improve cognition, mood, and psychological health. An increasing number of small-scale studies are exploring this topic as a primary outcome. After randomization to a high and a low n-3 PUFA diet, breast cancer survivors in the high n-3 PUFA group reported a significant decrease in pain, perceived stress, sleep, depression and fatigue after 6 weeks [13]. In men scheduled for radical prostatectomy, anxiety and depression scores decreased in participants randomized to EPA or placebo (sunflower oil) capsules for 1 year compared to baseline values [19]. No difference in quality of life (Extended Prostate Cancer Index Composite-26 and International Prostate Symptom Score) between groups was observed at 3, 6, 9 and 12 months after surgery [18]. In this patient group with low psychosocial symptoms, the only between-group difference observed was an improved cognitive impact score in the placebo group [19]. A retrospective analysis in lung cancer patients ($n = 100$) explored the effect of n-3 PUFAs on several well being factors. Half of the group received fish oil capsules and the other half received usual care for 6 months. The n-3 PUFA group had higher physical and emotional functioning scores and lower insomnia and constipation scores [16]. More well powered RCTs, with a biological measure of compliance are needed to explore the effects of n-3 PUFA supplementation on psychological well being.

CONSIDERATIONS AND FUTURE DIRECTIONS

Future studies must be sufficiently powered and of long enough duration to capture late developing impacts of cancer treatment. The dose of n-3 PUFAs should be one that produces measurable change in the proportion of EPA and DHA in circulation as a proxy for the tissue of interest during the measurement period. Adherence and reporting of adherence poses a challenge to interpreting study outcomes and comparing results across settings. Capsules appear to evoke better compliance than commercially available oral nutritional supplements, but actual intake versus prescribed intake are not universally reported. Additionally, individual response to n-3 PUFAs may vary because of differences in baseline n-3 PUFA status, sex, and genetics. Biological measures of n-3 PUFA status with or without patient-reported compliance measures would permit individualized assessment of changes in n-3 PUFA status to enable more confident study interpretation and would help to define a range of efficacious dosing towards achieving specific outcomes, generally thought to be between 2 and 4 g per day (amount of EPA and DHA in isolation not established) under different treatment regimens. In children, n-3 PUFAs are dosed based on body size (body weight in kilograms); however, this approach may also be feasible in adult populations. For example, doses based on muscle mass may reduce the variability of responses seen in past studies. Provision of parenteral sources of n-3 PUFAs in clinical settings has potential to rapidly elevate plasma n-3 PUFAs to levels thought to be efficacious.

Several caveats to studying oncology populations also exist that will require careful consideration for designing new definitive trials. Early interventions appear to be key for improving health and nutrition outcomes. de van der Schueren suggests that there may be specific windows of opportunity for better patient adherence to nutrition interventions, and that a sufficient duration is required to achieve a significant impact (i.e. short interventions are less effective) [57]. Capitalizing on this window for timing of a nutrition intervention should be considered when designing studies.

Effective symptom management is another key to success of any nutritional intervention and should be a component of standard of care at all centers. Stratifying by inflammatory status may reduce variability of response between patients. Nutritional intervention studies, including many reviewed here, are often inadequately powered. The sex ratio does not always reflect the prevalence of the specific cancer type. Exploring the endpoints that matter most to patients has not been addressed. Involvement of patient perspectives from initial to final steps of research leads to outcomes that are more meaningful to people with cancer. Addressing these limitations in future studies will inform for which patients n-3 PUFAs may be recommended.

CONCLUSION

Interventions with long-chain n-3 PUFAs in the oncology setting remain of intense interest. Clinical studies, albeit with limitations, reveal that n-3 PUFAs may benefit patients with cancers by lowering toxicity, maintaining physical function and nutritional status, controlling tumor growth, and improving tumor responses, and quality of life. Large-scale, population-based studies have yielded evidence for a protective effect of n-3 PUFAs on cancer survival. Promising upcoming mechanistic studies include those exploring the production of lipid mediators derived from n-3 PUFAs, the microbiome and mechanisms of n-3 PUFA effects during immunotherapy. Publications expected in the next 18 months will provide information on n-3 PUFA recommendations for cancer survivors and potentially enable appropriate recommendations for n-3 PUFA intakes for people with cancer.

Acknowledgements

The authors thank Dr Pamela Klassen for her critical review of the manuscript draft.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochem Soc Trans 2017; 45:1105–1115.
2. Klassen P, Cervantes M, Mazurak VC. N-3 fatty acids during chemotherapy: toward a higher level of evidence for clinical application. Curr Opin Clin Nutr Metab Care 2020; 23:82–88.
3. van der Meij BS, Mazurak VC. Fish oil supplementation and maintaining muscle mass in chronic disease: state of the evidence. Curr Opin Clin Nutr Metab Care 2020; 23:164–173.
4. Chang JPC, Tseng PT, Zeng BS, *et al.* Safety of supplementation of omega-3 polyunsaturated fatty acids: a systematic review and meta-analysis of randomized controlled trials. Adv Nutr 2023; 14:1326–1336.
5. Guo Y, Ma B, Li X, *et al.* n-3 PUFA can reduce IL-6 and TNF levels in patients with cancer. Br J Nutr 2023; 129:54–65.
6. Liu H, Chen J, Shao W, *et al.* Efficacy and safety of omega-3 polyunsaturated fatty acids in adjuvant treatments for colorectal cancer: a meta-analysis of randomized controlled trials. Front Pharmacol 2023; 14:1004465.
7. ■■ Wang Y, Liu K, Long T, *et al.* Dietary fish and omega-3 polyunsaturated fatty acids intake and cancer survival: a systematic review and meta-analysis. Crit Rev Food Sci Nutr 2023; 63:6235–6251.

Meta-analysis of 26 518 patients showing increased overall survival and cancer-specific survival as well as safety of n-3 PUFA.

8. Amiri Khosroshahi R, Heidari Seyedmahalle M, Zeraattalab-Motlagh S, *et al.* The effects of omega-3 fatty acids supplementation on inflammatory factors in cancer patients: a systematic review and dose-response meta-analysis of randomized clinical trials. Nutr Cancer 2024; 76:1–16.
9. Sasanfar B, Toorang F, Salehi-Abarghouei A. Effects of n-3 polyunsaturated fatty acid supplementation on appetite: a systematic review and meta-analysis of controlled clinical trials. Syst Rev 2024; 13:44.
10. Arsic A, Krstic P, Paunovic M, *et al.* Anti-inflammatory effect of combining fish oil and evening primrose oil supplementation on breast cancer patients undergoing chemotherapy: a randomized placebo-controlled trial. Sci Rep 2023; 13:6449.
11. Tawfik B, Dayao ZR, Brown-Glaberman UA, *et al.* A pilot randomized, placebo-controlled, double-blind study of omega-3 fatty acids to prevent paclitaxel-associated acute pain syndrome in breast cancer patients: Alliance A22_Pilot2. Support Care Cancer 2023; 31:637.
12. Kahlenberg ZB, Rodriguez MF, Brenner A, Kaklamani VG. Evaluating the impact of omega-3 free fatty acid supplementation on postoperative complications in obese postmenopausal women with estrogen receptor positive breast cancer. Am Surg 2023; 89:1144–1146.
13. Xu W, Finitsis D, Salner A, Judge M. Feasibility of investigational procedures and efficacy of a personalized omega-3 dietary intervention in alleviating pain and psychoneurological symptoms in breast cancer survivors. Pain Manag Nurs 2023; 24:78–88.
14. Gui L, Cheng M, Zheng M, *et al.* Effects of omega-3 fatty acid supplementation on nutritional status and inflammatory response in patients with stage II-III NSCLC undergoing postoperative chemotherapy: a double-blind randomized controlled trial. Front Nutr 2023; 10:1266584.
15. Tanaka I, Yano Y, Mori M, *et al.* Impact of serum eicosapentaenoic acid/arachidonic acid ratio on overall survival in lung cancer patients treated with pembrolizumab: a pilot study. Sci Rep 2024; 14:1384.
16. Zhang M, Liu C, Zhang X, *et al.* The impact of a diet rich in omega-3 fatty acids on the quality of life of patients with squamous cell lung cancer and comorbid depression: a retrospective study. Actas Esp Psiquiatr 2024; 52:445–452.
17. Fuller H, Race AD, Fenton H, *et al.* Plasma and rectal mucosal oxylipin levels during aspirin and eicosapentaenoic acid treatment in the seAFOod polyp prevention trial. Prostaglandins Leukot Essent Fatty Acids 2023; 192:102570.
18. Moussa H, Robitaille K, Pelletier JF, *et al.* Effects of concentrated long-chain omega-3 polyunsaturated fatty acid supplementation on quality of life after radical prostatectomy: a phase ii randomized placebo-controlled trial (RCT-EPA). Nutrients 2023; 15:1369.
19. Savard J, Moussa H, Pelletier JF, *et al.* Effects of omega-3 supplementation on psychological symptoms in men with prostate cancer: secondary analysis of a double-blind placebo-controlled randomized trial. Cancer Med 2023; 12:20163–20176.
20. ■ Lachance G, Robitaille K, Laaraj J, *et al.* The gut microbiome-prostate cancer crosstalk is modulated by dietary polyunsaturated long-chain fatty acids. Nat Commun 2024; 15:3431.

The role of the microbiome and modulation by n-3 PUFA was shown using an experimental model and human for the prevention of prostate cancer.

21. Abe K, Furukawa K, Shirai Y, *et al.* Prognostic significance of sarcopenia and eicosapentaenoic acid (EPA) levels in patients with unresectable pancreatic or biliary tract cancer. Cancer Diagn Progn 2024; 4:135–140.
22. Barbosa-Cortes L, Atilano-Miguel S, Martin-Trejo JA, *et al.* Effect of long-chain omega-3 polyunsaturated fatty acids on cardiometabolic factors in children with acute lymphoblastic leukemia undergoing treatment: a secondary analysis of a randomized controlled trial. Front Endocrinol 2023; 14:1120364.
23. Barbosa-Cortés L, Martínez-Vieyra X, Mejía-Aranguré JM, *et al.* Pilot study on the effect of supplementation with long-chain ω-3 polyunsaturated fatty acids on body composition in children with acute lymphoblastic leukemia: randomized clinical trial. Clin Nutr 2023; 42:1759–1769.
24. Liu Z, Huang H, Xie J, *et al.* Circulating fatty acids and risk of hepatocellular carcinoma and chronic liver disease mortality in the UK Biobank. Nat Commun 2024; 15:3707.

25. O'Keefe EL, O'Keefe JH, Tintle NL, *et al.* Circulating docosahexaenoic acid ▪▪ and risk of all-cause and cause-specific mortality. Mayo Clin Proc 2024; 99:534–541.

Used the UK biobank as a resource to reveal an association between all-cause survival and cancer-related survival and DHA levels.

26. Zhang Y, Sun Y, Yu Q, *et al.* Higher ratio of plasma omega-6/omega-3 fatty ▪▪ acids is associated with greater risk of all-cause, cancer, and cardiovascular mortality: a population-based cohort study in UK Biobank. eLife 2024; 12: R90132.

Used the UK biobank as a resource to reveal as association between all-cause and cancer-related survival and n-3 PUFA.

27. Morsy BM, El Domiaty S, Meheissen MAM, *et al.* Omega-3 nanoemulgel in prevention of radiation-induced oral mucositis and its associated effect on microbiome: a randomized clinical trial. BMC Oral Health 2023; 23:612.
28. Seethaler B, Lehnert K, Yahiaoui-Doktor M, *et al.* Omega-3 polyunsaturated fatty acids improve intestinal barrier integrity-albeit to a lesser degree than short-chain fatty acids: an exploratory analysis of the randomized controlled LIBRE trial. Eur J Nutr 2023; 62:2779.
29. Omega-3 and vitamin D supplementation in breast cancer women. Clinicaltrials.gov identifier: NCT05331807. Updated 9 May 2024. Available at: https://clinicaltrials.gov/study/NCT05331807. [Accessed 1 September 2024]
30. Impact of omega 3 fatty acid supplementation on aromatase in obese subjects. Clinicaltrials.gov identifier: NCT02538484. Updated 17 July 2023. Available at: https://clinicaltrials.gov/study/NCT02538484. [Accessed 1 September 2024]
31. Deep-sea fish oil for prevention of acute radiation-induced esophagitis. Clinicaltrials.gov identifier: NCT06392971. Updated 5 January 2024. Available at: https://clinicaltrials.gov/study/NCT06392971. [Accessed 1 September 2024]
32. Immunonutritional supplement after total gastrectomy in patients with stage III gastric cancer (CRUCIAL). Clinicaltrials.gov identifier: NCT05253716. Updated 29 August 2022. Available at: https://clinicaltrials.gov/study/NCT05253716. [Accessed 1 September 2024]
33. Patients with locally advanced gastric cancer. Clinicaltrials.gov identifier: NCT06047158. Updated 21 September 2023. Available at: https://clinicaltrials.gov/study/NCT06047158. [Accessed 1 September 2024]
34. The effects of n-3 LCPUFAs in patients with colorectal cancer. Clinicaltrials.gov identifier: NCT04699760. Updated 7 January 2021. Available at: https://clinicaltrials.gov/study/NCT04699760. [Accessed 1 September 2024]
35. Peripheral neuropathy in colorectal cancer. Clinicaltrials.gov identifier: NCT05404230. Updated 5 September 2023. Available at: https://clinicaltrials.gov/study/NCT05404230. [Accessed 1 September 2024]
36. Supplementation of n-3 PUFA in the modulation of lean mass in patients with lung cancer receiving a high-protein diet. Clinicaltrials.gov identifier: NCT04965129. Updated 17 May 2024. Available at: https://clinicaltrials.gov/study/NCT04965129. [Accessed 1 September 2024]
37. Multimodal Prehabilitation for Lung Cancer Surgery (MMP-LUNG) Clinicaltrials.gov identifier: NCT05955248. Updated 21 July 2023. Available at: https://clinicaltrials.gov/study/NCT05955248. [Accessed 1 September 2024]
38. Tumor nutritional therapy in the first-line treatment of stage IV. Clinicaltrials.gov identifier: NCT06356701. Updated 10 April 2024. Available at: https://clinicaltrials.gov/study/NCT06356701. [Accessed 1 September 2024]
39. Vit D3 and omega 3 in chemo induced neuropathy. Clinicaltrials.gov identifier: NCT02294149. Updated 7 April 2015. Available at: https://clinicaltrials.gov/study/NCT02294149. [Accessed 1 September 2024]
40. Effects of EPA in men with biochemical recurrence or progression of prostate cancer (RCT-EPAII-BCR) Clinicaltrials.gov identifier: NCT03753334. Updated 21 September 2023. Available at: https://clinicaltrials.gov/study/NCT03753334. [Accessed 1 September 2024]
41. Anti-Inflammatory Diet in BRC Patients on Aromatase Inhibitors (AID). Clinicaltrials.gov identifier: NCT06214598. Updated 9 May 2024. Available at: https://clinicaltrials.gov/study/NCT06214598. [Accessed 1 September 2024]
42. 12-mo intervention of low vs. high dose omega-3 on eicosanoids and inflammatory markers. Clinicaltrials.gov identifier: NCT02295059. Updated 23 May 2024. Available at: https://clinicaltrials.gov/study/NCT02295059. [Accessed 1 September 2024]
43. Rushing BR, Wiggs A, Molina S, *et al.* Metabolomics analysis reveals novel targets of chemosensitizing polyphenols and omega-3 polyunsaturated fatty acids in triple negative breast cancer cells. Int J Mol Sci 2023; 24:4406.
44. Gurav P, Patade T, Hajare S. Kedar RN. n-3 PUFAs synergistically enhance the efficacy of doxorubicin by inhibiting the proliferation and invasion of breast cancer cells. Med Oncol 2023; 41:2.
45. Augimeri G, Fiorillo M, Morelli C, *et al.* The omega-3 docosahexaenoyl ethanolamide reduces CCL5 secretion in triple negative breast cancer cells affecting tumor progression and macrophage recruitment. Cancers 2023; 15:819.
46. Zhang H, Chen H, Yin S, *et al.* Docosahexaenoic acid reverses PD-L1-mediated immune suppression by accelerating its ubiquitin-proteasome degradation. J Nutr Biochem 2023; 112:109186.
47. Pettersen CHH, Samdal H, Sætrom P, *et al.* The salmon oil OmeGo reduces viability of colorectal cancer cells and potentiates the anti-cancer effect of 5-FU. Mar Drugs 2023; 21:636.
48. Xu Q, Zhang Z, Tang M, *et al.* Endogenous production of ω-3 polyunsaturated fatty acids mitigates cisplatin-induced myelosuppression by regulating NRF2-MDM2-p53 signaling pathway. Free Radic Biol Med 2023; 201:14–25.
49. Yang X, Li W, Li S, *et al.* Fish oil-based microemulsion can efficiently deliver oral peptide blocking PD-1/PD-L1 and simultaneously induce ferroptosis for cancer immunotherapy. J Control Release 2024; 365:654–667.
50. Xiao X, Luo S, Huang J, *et al.* Synergistic effects of Ω-3 polyunsaturated fatty acid supplementation and programmed cell death protein 1 blockade on tumor growth and immune modulation in a xenograft model of esophageal cancer. Clin Nutr ESPEN 2024; 61:308–315.
51. Fernando W, Clark RF, Rupasinghe HPV, *et al.* Phloridzin docosahexaenoate inhibits spheroid formation by breast cancer stem cells and exhibits cytotoxic effects against paclitaxel-resistant triple negative breast cancer cells. Int J Mol Sci 2023; 24:14577.
52. Podpeskar A, Crazzolara R, Kropshofer G, *et al.* Omega-3 fatty acids and their role in pediatric cancer. Nutrients 2021; 13:1800.
53. Zhang D, Gu M. Effect of supplementation with long-chain ω-3 polyunsaturated fatty acids on body composition in children with acute lymphoblastic leukemia. Clin Nutr 2023; 42:2068–2069.
54. Silva JMLD, Barros WMA, Silva MLD, *et al.* Letter to the editor: pilot study on the effect of supplementation with long-chain ω-3 polyunsaturated fatty acids on body composition in children with acute lymphoblastic leukemia: randomized clinical trial. Clin Nutr 2023; 42:2588–2589.
55. Hull MA, Sprange K, Hepburn T, *et al.* Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFOod Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2 × 2 factorial trial. Lancet 2018; 392:2583–2594.
56. Serhan CN, Bäck M, Chiurchiù V, *et al.* Expert consensus report on lipid mediators: role in resolution of inflammation and muscle preservation. FASEB J 2024; 38:e23699.
57. de van der Schueren MAE, Laviano A, Blanchard H, *et al.* Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. Ann Oncol 2018; 29:1141–1153.

