n-3 PUFA can reduce IL-6 and TNF levels in patients with cancer

Yongzhong Guo[1]†, Bo Ma[2]†, Xinhua Li[3]†, Hui Hui[4], Yun Zhou[4], Na Li[4] and Xiaomei Xie[4]*

[1]*Department of Respiratory and Critical Care Medicine, Xuzhou Central Hospital, The Xuzhou School of Clinical Medicine of Nanjing Medical University, Xuzhou Clinical School of Xuzhou Medical University, Xuzhou, Jiangsu, People's Republic of China*
[2]*Department of Orthopedics, the First Affiliated Hospital of Soochow University, Orthopedic Institute, Soochow University, Suzhou, Jiangsu, People's Republic of China*
[3]*Shanxi Key Laboratory of Stem Cell for Immunological Dermatosis, Institute of Dermatology, Taiyuan City Center Hospital, Taiyuan Central Hospital of Shanxi Medical University, Taiyuan, Shanxi, People's Republic of China*
[4]*Department of Radiotherapy, Xuzhou Central Hospital, The Xuzhou School of Clinical Medicine of Nanjing Medical University, Xuzhou Clinical School of Xuzhou Medical University, Xuzhou, Jiangsu, People's Republic of China*

Abstract

Current studies on inhibitory effects of *n*-3 PUFA on pro-inflammatory cytokines have inconsistent results. Thus, a meta-analysis of randomised controlled trials was conducted to identify the effects of *n*-3 PUFA administration on circulating IL-6 and TNF in patients with cancer. Studies that examined the effects of *n*-3 PUFA administration on circulating IL-6 and TNF in patients with cancer were identified by searching PubMed and EMBASE from January 1975 to February 2021. Differences in *n*-3 PUFA administration and control conditions were determined by calculating standardised mean differences (SMD) with 95 % CI. Twenty studies involving 971 patients met the inclusion criteria. The overall SMD were 0·485 (95 % CI 0·087, 0·883) for IL-6 and 0·712 (95 % CI 0·461, 0·962) for TNF between *n*-3 PUFA administration and control conditions. Sources of heterogeneity were not found through subgroup and meta-regression analyses. Publication bias was observed in TNF with a slight contribution to the effect size. *n*-3 PUFA can reduce circulating IL-6 and TNF levels in patients with cancer. Results supported the recommendation of *n*-3 PUFA as adjuvant therapy for patients with cancer, possibly excluding head and neck cancer, owing to their anti-inflammatory properties.

Key words: PUFA: IL-6: TNF: Cancer: Meta-analysis

Increasing evidence on the role of inflammation in carcinogenesis and cancer development[1–4] has led to the proposition that treatments targeting deregulated inflammatory responses can be used as alternative strategies for cancer prevention and therapy[3–5]. Within this perspective, *n*-3 PUFA, as essential nutrients for normal metabolism, have attracted considerable interest in cancer-preventive and anticancer effects due to their potential role in suppressing and resolving inflammation[6–10]. Indeed, the use of *n*-3 PUFA for patients with cancer has been recommended by the European Society for Parenteral and Enteral Nutrition to patients with cancer, although the evidence is weak[11].

n-3 PUFA exert effects against various inflammatory conditions or disorders, including cancer[6–10,12]. However, inconsistencies regarding the inhibitory effects of *n*-3 PUFA on systemic inflammation in patients with cancer have been found in the literature, weakening the potential use of *n*-3 PUFA in cancer prevention and treatment. Numerous inflammatory cytokines directly contribute to carcinogenesis, and most of them are largely confined to experimental research and have limited significance in clinical practice[2,3,13,14]. Among them, IL-6 and TNF are the most extensively studied inflammatory cytokines in clinical studies to identify associations between systemic inflammation and cancer. However, findings on the evolution of circulating IL-6 and TNF levels after *n*-3 PUFA use in patients with cancer are inconsistent, including those of meta-analyses[15–20]. In view of the increasing benefits to cancer treatment, only mild side effects and no convincingly serious safety issues, determining the effects of *n*-3 PUFA administration on IL-6 and TNF levels in cancer patients has clinical importance[9].

Previous meta-analyses focused on digestive system cancer and included a small number of studies (two to seven per analysis) and sample size (only eighty-six patients in some studies)[15–20]. Thus, they are prone to selection and information

---

Abbreviations: RCT, randomised controlled trial; SMD, standardised mean differences.

* **Corresponding author:** Xiaomei Xie, email gxxm2007@163.com

† These authors contributed equally to this work

bias. Moreover, the potential effects of relevant variables on IL-6 and TNF levels cannot be quantitatively identified by subgroup and meta-regression analyses because of the limited number of included studies. Since the publication of previous meta-analyses, several high-quality randomised controlled trials (RCT) have been conducted to explore the effects of *n*-3 PUFA on IL-6 and TNF levels but did not yield consistent results. Thus, a meta-analysis of RCT was conducted for the evaluation of the effects of *n*-3 PUFA administration on circulating IL-6 and TNF levels in patients with various types of cancer and potential impact of relevant variables, with particular concern to the optimal patients and regimens for which *n*-3 PUFA administration may be highly beneficial.

Methods and materials

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[21].

Literature search and selection

The PubMed and EMBASE were searched for RCT published from January 1975 to February 2021 and updated in September 2021. The search was limited to RCT that enrolled adult humans and had no language restrictions. The following search terms were included, with combined free text and subject terms: 'inflammation' or 'inflammatory;' 'interleukin-6' or 'IL-6;' 'tumor necrosis factor or 'TNF;' 'fatty acids' or 'alpha-linoleic acid (ALA)' or 'eicosapentaenoic acid (EPA)' or 'docosahexaenoic acid (DHA);' and 'cancer' or 'carcinoma' or 'neoplasm' or 'tumor' or 'tumour' or 'malignancy'. The reference lists of relevant publications were manually searched for additional studies.

The search followed the Patient, Intervention, Comparison, Outcome (PICO) strategy: (1) patient (P): patients with diagnosed cancer based on acceptable criteria; (2) intervention (I): *n*-3 PUFA administration (regardless of type and dose); (3) comparison (C): non-*n*-3 PUFA administration or placebo; and (4) outcome (O): circulating IL-6 and TNF levels.

If multiple studies reported outcomes on the same patient group, the one with the largest sample size was included. Abstracts, case reports, editorials, expert opinions, letters, animal studies and reviews without original data were excluded.

Data extraction and quality assessment

Two investigators independently extracted information from all eligible studies according to a standardised protocol. Disagreements were resolved through consensus with a third investigator. Data extracted from each study included the name of the first author, year of publication, nation, study design, sample size, patient inclusion criteria, cancer site, inflammatory markers, intervention, therapy duration, primary concurrent treatment, patient's age and BMI. When only standard errors instead of standard deviations were provided in the study, standard deviation was calculated by multiplying the standard error by the square root of the sample size. In addition, some studies provided medians and ranges instead of means and standard deviation; the corresponding means and standard deviation were calculated with the method described by Hozo et al.[22]

The methodological quality of the RCT was evaluated by using the Jadad scale ranging from 0 to 7 points, including the following aspects: randomisation (0, 1 or 2), double-blinding (0, 1 or 2), concealment of allocation (0, 1 or 2), and withdrawals and dropouts (0 or 1)[23]. A score of ≥ 4 indicates high quality[24]. Two investigators rated each study independently and subsequently assigned a score to minimise selection bias. Disagreements were resolved through a consensus with a third investigator.

Statistical analysis

The meta-analysis was conducted using Stata statistical software (version 10.0, Stata Corporation). Given the diversity in the measurement and reporting of inflammatory markers among various laboratories, the computation of the summary estimates was used with a standardised mean difference (SMD) instead of the absolute levels of inflammatory markers. Heterogeneity across studies was tested using Q and I^2 statistics. Significant heterogeneity was indicated by $P_{heterogeneity} < 0.10$ or $I^2 > 60\%$. A random-effects model was used when significant heterogeneity was observed; otherwise, a fixed-effect model was used to analyse the pooled results. Sensitivity analyses by changing the eligibility criteria, including the omission of one study at a time, were conducted to explore the robustness of the pooled results.

Subgroup analyses grouped by study design (double-blinded and non-double-blinded), sample size (≤ 40 and > 40), Jadad score (≤ 3 and ≥ 4), study area (America, Asia and Europe), cancer site (head and neck, gastric, colorectal, and other), fatty acid types (*n*-3 PUFA, DHA and EPA combined, and EPA), administration routes (oral, nasal and intravenous), therapy duration (≤ 1 month and > 1 month), primary concurrent treatment (chemotherapy, operation and others) and patient age (≤ 60 years and > 60 years) were performed using random-effects model to evaluate the effects of these variables on inflammation levels, as well as the possible sources of heterogeneity.

Meta-regression analyses (≥ 10 studies for each variable) were used to determine whether some relevant variables, including publication year, study design, Jadad score, sample size, study area, fatty acid types, administration routes, therapy duration, primary concurrent treatment, basic inflammation levels, patient age and BMI, were the possible sources of heterogeneity, as well as the existence of a linear relationship with inflammatory marker change.

Publication bias was evaluated visually by funnel plots and statistically by Egger's and Begg's tests. If significant publication bias was presented, the 'trim-and-fill' method was used to examine the expected number of studies needed to correct the asymmetry of funnel plots and compute the adjusted pooled result. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Characteristics of included studies

A detailed flow chart of the study selection process is outlined in Fig. 1. A total of 115 potentially related articles were identified
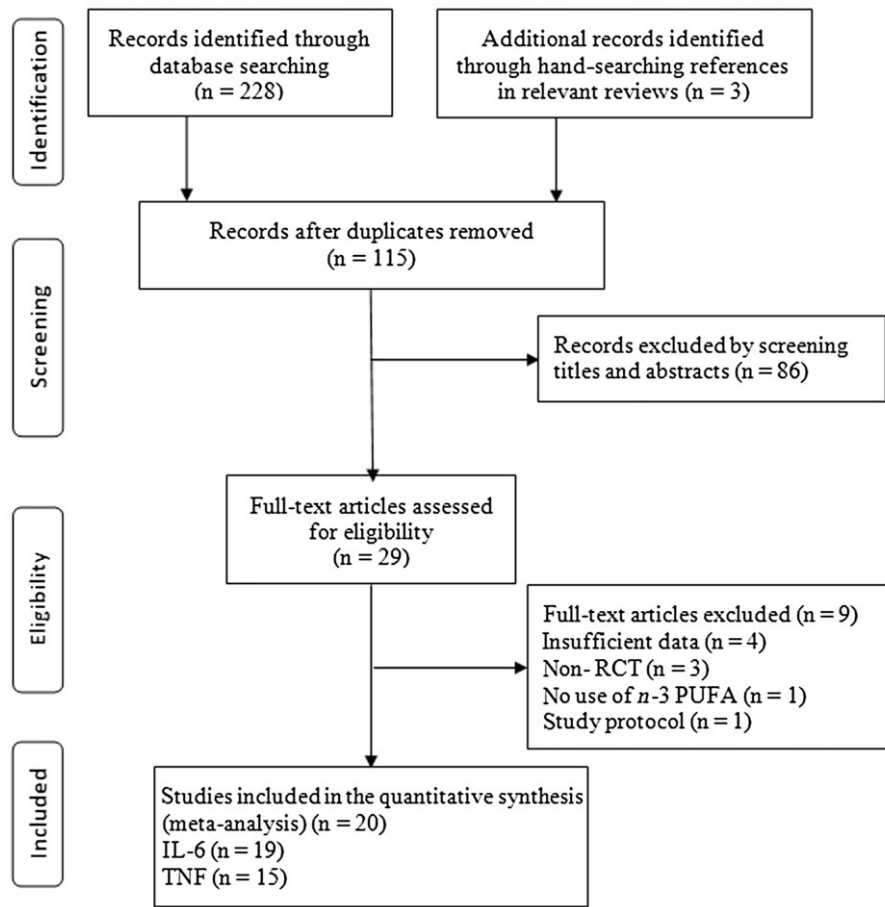
Fig. 1. Flow diagram of study selection.

through an initial online search. After the titles and abstracts were reviewed, twenty-nine articles were selected and further examined. Nine of the twenty-nine articles were excluded for the following reasons: four had no original data[25–28], three were not RCT[29–31], one did not use *n*-3 PUFA[32] and one was a study protocol[33]. Therefore, twenty articles that satisfied the inclusion criteria were included in the meta-analysis: nineteen for IL-6[34–52] and fifteen for TNF[36–41,43,44,46,48–53]. Table 1 provides the detailed characteristics of the included studies.

Results for IL-6

The pooled result indicated a significant decrease in IL-6 level after *n*-3 PUFA administration and showed significant heterogeneity (Fig. 2). Sensitivity analysis by omitting one RCT at a time showed that SMD ranged from 0·378 (95 % CI 0·033, 0·753) to 0·568 (95 % CI 0·175, 0·961) when the studies of Wu 2001[36] and Felekis 2010[39] were omitted. After five studies were removed, in which means and standard deviations were extracted by reading the graphs or calculating the medians and interquartile ranges[35,42,45,47,50], a significant decrease in IL-6 was observed (SMD, 0·573; 95 % CI 0·092, 1·053) and the heterogeneity remained significant ($P_{\text{heterogeneity}} < 0·001$; $I^2 = 90·5$ %). Additional analysis by including two

non-RCT[29,30] showed a similar result in IL-6 after *n*-3 PUFA administration (SMD, 0·975; 95 % CI 0·386, 1·564) with significant heterogeneity ($P_{\text{heterogeneity}} < 0·001$; $I^2 = 94·7$ %).

Subgroup analyses suggested significant differences existed when grouping was performed according to study area, cancer site, fatty acid types and primary concurrent treatment (Table 2). No significant linear relationship between IL-6 and some relevant variables was observed through meta-regression analysis (Table 3). The possible sources of heterogeneity were not found by subgroup and meta-regression analyses (Tables 2 and 3).

No publication bias was observed from funnel plot and associated statistics ($P_{\text{Begg}} = 0·484$; $P_{\text{Egger}} = 0·319$) (Fig. 4).

Results for TNF

A remarkable decrease in TNF was observed after *n*-3 PUFA administration with significant heterogeneity (Fig. 3). Sensitivity analysis by omitting one RCT at a time showed that SMD ranged from 0·642 (95% CI 0·414, 0·870) to 0·771 (95% CI 0·537, 1·005) when the RCT of Finocchiaro 2012[44] and Felekis 2010[39] were omitted. A similar result was obtained after the study of Ryan 2009[41] was removed, in which data were extracted by reading the graph (SMD, 0·745; 95% CI 0·480, 1·011). Pooled analysis by including one non-RCT[29] using

Table 1. Characteristics of studies included in meta-analysis

Study	Location	Design	Cancer Type	Eligibility Criteria	Therapy Duration	Dosage Form	Intervention (Per d)	Concurrent Treatment	Age (years) Mean	SD	BMI (kg/m²) Mean	SD	Drop off	Jadad Score
Furukawa 1999	Japan	RCT, DB	Oesophageal	Esophagectomy with thoracotomy	17 d	TPN	1·8 g EPA	PO	58·0	4·0	NR		0	2
Gianotti 1999	Italy	RCT, DB	Stomach or colorectum	18–75 years, adenocarcinoma	7 d	EN	(10·5 % n-3 PUFA + 8·3 % n-6 PUFA) g/l	PO	62·5 60·9†	11·3* 12·5†	NR		5	5
Wu 2001	China	RCT, DB	Gastrointestinal	Major abdominal surgery	8 d	EN	1·896 g EPA + 0·72 g DHA	PO	55·2 52·6	12·1* 9·8†	NR		0	3
Chen 2005	China	RCT	Gastric carcinoma	Major elective surgery	9 d	EN	4·17 g/l (n-6:n-3) PUFA (3·45:1)	PO	59·0	12·6	NR		0	1
Casas-Rodera 2008	Spain	RCT	Oral and laryngeal	NR	14·5 d	EN	2·8 g (n-6:-n-3) PUFA (0·7:1)	PO	54·3 50·1	13·0* 13·8†	NR		0	2
Liang 2008	China	RCT	Colorectal	Stage I–III, radical resection	7 d	TPN	0·2 g/kg n-3 PUFA	PO	55·8 59·2	10·1* 10·6†	23·4 23·9	2·4* 2·8†	1	6
Ryan 2009	Ireland	RCT, DB	Oesophageal	Resectable	26 d	EN	4·5 g/l EPA 1·9 g/l DHA	PO	62·0 65·7	11·0* 9·0†	24·6 27·1	3·4* 4·1†	0	4
Dimitrios 2010	Greece	RCT, DB	Head and neck	Histologically diagnosis of squamous cell carcinoma for surgical treatment, no CT or RT	8 d	Capsule	Arginine, RNA, n-3 PUFA	PO	61·0 63·2	3·8* 3·9†	NR		0	5
Silva 2012	Brazil	RCT	Colorectal	> 18 years, anthropometrics, dietary and biochemical assessment	9 weeks	Capsule	0·6 g PUFA	CT	50·1 54·3	8·2* 9·3†	26·7 24·6	5·8* 2·8†	5	2
Finocchiaro 2012	Italy	RCT, DB, multi-centre	Lung	18–70 years, advanced stage, ≤ 10 % weight loss, CT, life expectancy ≥ 2 months, KPS ≥ 80	66 d	Capsule	0·85 g (EPA + DHA) (3:2)	CT	58·1 60·6	6·7* 7·4†	26·2 25·0	7·0* 3·9†	6	5
Mocellin 2013	Brazil	RCT	Colorectal	>19 years, histopathological diagnosis, CT indication	9 weeks	Capsule	0·6 g (EPA + DHA) (3:2)	CT	54·5	9·8	NR		1	3
Kanat 2013	Turkey	RCT	Malignancy at any site	≥ 18 years with histological/radiological/ clinical, advanced stage, KPS ≥ 70 %, loss ≥ 5 % body weight, life expectancy ≥ 3 months	3 months	Capsule	2·2 g EPA	CT and/or CRT	60·8	12·9	20·6	3·5	7	3
Roca-Rodriguez 2014	Spain	RCT	ENT	Stage III–IV	3 months	EN	6 g n-3 PUFA	RT	61·0 61·1	14·7* 10·7†	25·3 27·5	4·6* 4·0†	0	2
Wang 2015	China	RCT	Gastric	Radical resection	7 d	EN	0·2 g/kg n-3 PUFA	PO	59·8 60·1	2·1* 1·8†	NR		0	3
Carvalho 2017	Brazil	RCT, DB	Oral cavity	40–75 years, histopathological diagnosis, non-treatment, malnutrition or nutritional risk	4 weeks	EN	2 g EPA	Antineoplastic pretreatment	57·3 53·3	9·1* 8·8†	20·7 22·6	3·4* 4·3†	0	6
Golkhalkhali 2018	Malaysia	RCT, DB	Colorectal	CT	8 weeks	Capsule	2 g (EPA + DHA)	CT	58·0 (median)		21·8 23·0	4·1* 4·3†	0	4
Solis-Martinez 2018	Mexico	RCT	Head and neck	Cytologically diagnosed, squamous cell cancer, start any antineoplastic treatment	6 weeks	Polymeric diet	2 g EPA	No	60·0 58·0	14·0* 14·0†	22·6 24·0	4·6* 4·2†	0	2
Feijo 2019	Brazil	RCT, open longitudinal	Gastric	40–65 years, pretreatment	30 d	EN	3·2 g (EPA + DHA)	No	58·0 (median) 22·8		24·2	20·4–26·3* 20·1–28·3†	15	4

Y. Guo *et al.*

Table 1. (*Continued*)

Study	Location	Design	Cancer Type	Eligibility Criteria	Therapy Duration	Dosage Form	Intervention (Per d)	Concurrent Treatment	Age (years) Mean	SD	BMI (kg/m²) Mean	SD	Drop off	Jadad Score
Haidari 2020	Brazil	RCT, DB, placebo-controlled	Colorectal	> 18 years, stage II or III, receive 2 weeks cycles of CT	8 weeks	Capsule	0·66 g *n*-3 PUFA	CT	56·8 59·9	10·6* 8·8†	24·2 25·4	2·9* 3·5†	15	7
Li 2020	China	RCT, DB, single centre	Gastric	18–80 years, histopathological diagnosis, subtotal or total gastrectomy	5 d	EN	(0·025 g EPA + 0·018 g DHA)/kg	No	57·3 55·0	10·2* 9·6†	NR		6	5

RCT, randomised controlled trials; DB, double-blind; TPN, total parenteral nutrition; PO, postoperation; NR, not reported; EN, enteral nutrition; CT, chemotherapy; RT, radiotherapy; KPS, karnofsky performance status; ENT, ear, nose and throat.
* Treatment group.
† Control group.

random-effects model revealed similar decrease in TNF levels after *n*-3 PUFA administration (SMD, 0·840; 95 % CI 0·508, 1·172) with significant heterogeneity ($P_{heterogeneity} < 0·001$; $I^2 = 81·9\%$).

Subgroup analyses revealed the differences in sample size, Jadad score and cancer site might affect *n*-3 PUFA efficacy (Table 4). The sources of heterogeneity were not found by subgroup (Table 4) and meta-regression (Table 3) analyses.

The funnel plot (Fig. 4) and Begg's ($P = 0·038$) and Egger's test ($P = 0·094$) indicated the occurrence of publication bias for TNF. The 'trim-and-fill' method showed the need for five additional studies to correct the funnel plot asymmetry (Fig. 4). The SMD corrected using the fixed- and random-effects models were 0·469 (95 % CI 0·337, 0·601) and 0·467 (95 % CI 0·192, 0·742), respectively, which indicated the slight contribution of publication bias to the pooled results.

Discussion

This meta-analysis assessed the effects of *n*-3 PUFA administration on circulating IL-6 and TNF levels in patients with cancer. The results indicated that *n*-3 PUFA can reduce IL-6 and TNF levels. Sensitivity analyses by changing the eligibility criteria further strengthened the robustness of the results.

n-3 PUFA possess anti-inflammatory and inflammation-resolving activities, possibly related to the inhibition of IL-6 and TNF production. The inhibitory effects of *n*-3 PUFA on IL-6 and TNF have been reported in multiple inflammatory diseases. However, the results are inconsistent in patients with cancer. The current finding supported the role of *n*-3 PUFAs in reducing circulating IL-6 and TNF levels in patients with cancer. Partially consistent with current results, most previous meta-analyses reported significant decrease in IL-6[15–18] and TNF[16,18,19], whereas few reported non-significant changes in IL-6[19] and TNF[17] after *n*-3 PUFA administration in digestive system cancer. Similar findings were observed in breast, lung and colorectal cancers examined in previous non-RCT[31,54–56]. Favourable evidence were provided by *in vitro* studies. Findings showing that *n*-3 PUFA use can decrease IL-6 and TNF secretion were reported in various human[57–59] and other mammary cultured cells[60]. Although not affected IL-6 and TNF secretion, *n*-3 PUFA can promote pro-resolving responses in human monocytes[61]. Based on current published literature, the effects of reducing IL-6 and TNF levels in patients with cancer should be regarded as convincing.

When the suppressive action of *n*-3 PUFA on inflammatory cytokines (IL-6 and TNF) in patients with cancer was established, the pros and cons of *n*-3 PUFA use should be weighed.

IL-6 is a multifaceted pleiotropic cytokine mainly produced by cancer and stromal cells in patients with cancer and has a wide range of target cells because of its trans-signalling mechanism. IL-6 has carcinogenic actions in experimental cancer models and patients with cancer[14,62–64]. Raised IL-6 levels indicate poor prognosis in patients with several types of cancer[3]. Anti-IL-6 therapy can target cancer by suppressing cancer growth, metastasis, metabolism and cachexia[3,5,64].
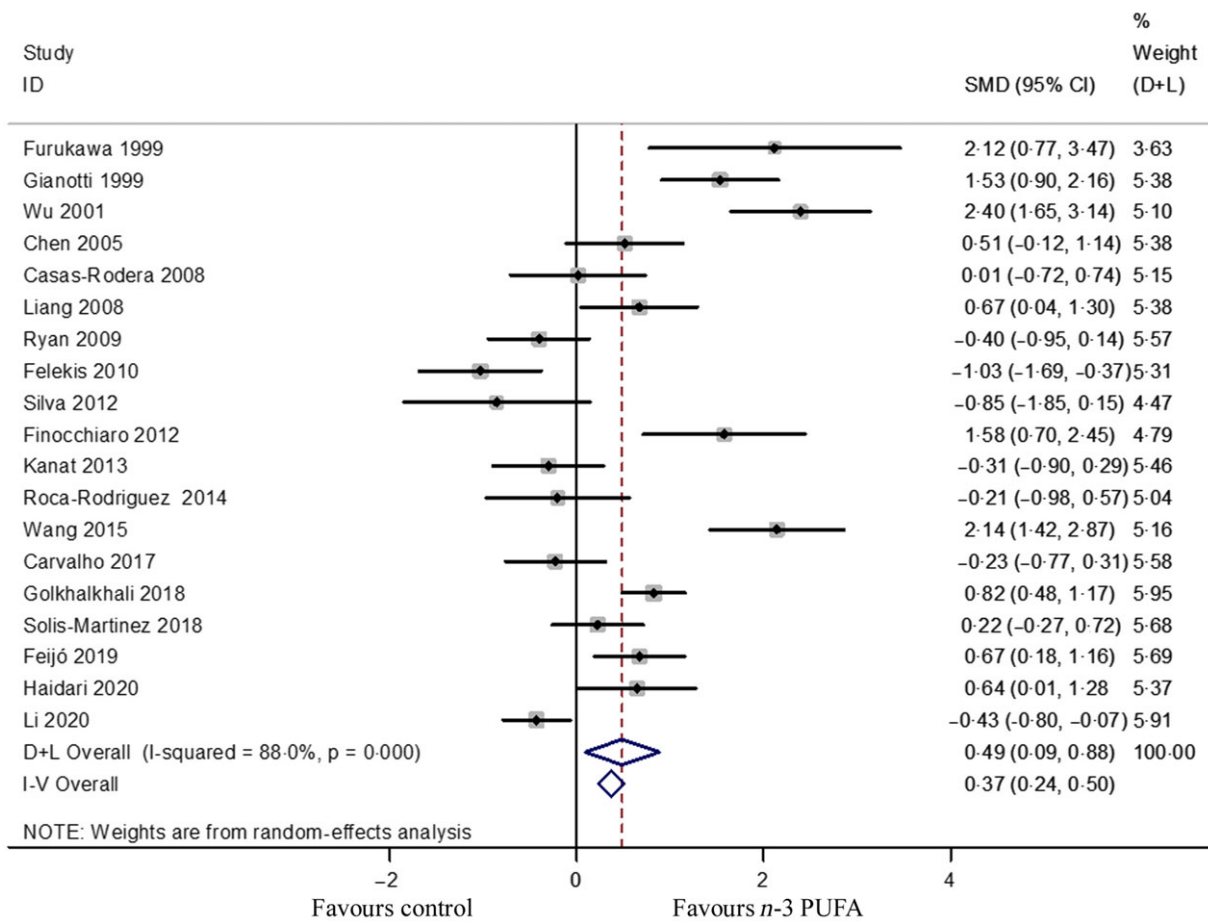
Fig. 2. Meta-analysis of *n*-3 PUFA administration on IL-6 in cancer patients. CI, confidence interval; SMD, standardized mean difference.

TNF is another key cytokine that associates inflammation with cancer. TNF has been initially found to have anticancer functions because of its capability to induce haemorrhagic necrosis in tumours. Existing data indicate that TNF is a poor apoptosis inducer with weak cytotoxic or cytostatic effects on malignant cells[65]. Only high-dose TNF administration can be used as a cytotoxic agent to kill tumour cells[65,66]. Moreover, TNF is a pro-cancer cytokine that favours tumour growth and metastasis[14,65]. Elevated circulating TNF concentration and expression are present in various pre-cancerous and malignant diseases. Chronic, low-level TNF exposure is linked to a pro-malignant phenotype (growth, invasion and metastasis)[66].

Regardless of the underlying mechanism linking IL-6 and TNF with cancer, substantial evidence now exists to suggest that reductions in IL-6 and TNF levels are associated with the benefits of cancer treatment.

Conforming to the results of subgroup analyses, the anti-inflammatory action of *n*-3 PUFA may be subject to multiple factors. The disparity influence of race and ethnicity in various aspects of cancer, including treatment response, was observed[67,68]. Compared with their American and European counterparts, Asians can attain more benefits from *n*-3 PUFA administration. Additionally, differences in serum IL-6 and TNF levels were reported among people with different ethnic origins or regions[69] and people with different serum *n*-3 PUFA levels[70]. Previous studies supported different effects of *n*-3 PUFA administration on C-reactive protein in diverse populations[20]. The disparate impacts of *n*-3 PUFA on circulating IL-6 and TNF in various regions were understandable, although no study directly compared the effects of *n*-3 PUFA administration on IL-6 and TNF levels in diverse populations.

A site-specific association between cancer and inflammation was reported[71,72]. The present analysis supported the diverse effects of cancer sites on IL-6 and TNF levels. Unexpectedly, an increasing trend in IL-6 and a borderline result for TNF were observed in head and neck cancer. Chronic inflammation involving IL-6 and TNF was related to the development and progression of head and neck cancer[73]. None of the included RCT reported remarkable increases in IL-6 and TNF in head and neck cancer[38,39,45,47,49]. According to current knowledge, the present results for IL-6 and TNF in head and neck cancer should be interpreted with caution. The possible reasons are as follows: firstly, the power to disclose these potential benefits of the therapy because of the small sample size is insufficient. Secondly, the possibility of low IL-6 and TNF levels in head and neck cancer minimises the extent of their reduction. Finally, substantial effects of *n*-3 PUFA are lacking.

Table 2. The results of subgroup analyses for IL-6

Subgroup	No. of study/patient	Heterogeneity P; I^2 (%)	Random effects SMD	95 % CI	Fixed effects SMD	95 % CI	$P_{subgroup}$
Design							
DB	10/583	0·000; 91·8	0·635	−0·001, 1·272	0·360	0·187, 0·533	0·852
Non-DB	9/376	0·000; 79·8	0·346	−0·132, 0·823	0·386	0·176, 0·596	
Sample size							
≤ 40	8/233	0·000; 82·1	0·288	−0·366, 0·943	0·188	−0·082, 0·458	0·128
> 40	11/726	0·000; 90·8	0·614	0·097, 1·132	0·429	0·276, 0·583	
Jadad score							
≤ 3	9/318	0·000; 89·4	0·592	−0·160, 1·343	0·455	0·217, 0·694	0·401
≥ 4	10/641	0·000; 87·8	0·405	−0·070, 0·880	0·332	0·171, 0·493	
Study area							
America	5/242	0·017; 66·6	0·174	−0·287, 0·636	0·243	−0·014, 0·500	0·032
Asia	8/492	0·000; 91·8	0·923	0·218, 1·628	0·546	0·357, 0·735	
Europe	6/225	0·000; 89·1	0·232	−0·616, 1·081	0·142	−0·135, 0·419	
Cancer sites							
Head and neck	5/212	0·055; 56·8	−0·227	−0·653, 0·199	−0·189	−0·462, 0·084	< 0·001
Oesophageal	2/67	0·001; 91·4	0·779	−1·688, 3·246	−0·049	−0·554, 0·456	
Gastric	4/273	0·000; 93·0	0·693	−0·305, 1·690	0·306	0·057, 0·555	
Colorectal	4/238	0·022; 68·9	0·459	−0·085, 1·004	0·648	0·384, 0·912	
Others	4/169	0·000; 91·6	1·285	0·074, 2·495	1·106	0·761, 1·450	
Fatty acid types							
EPA	6/254	0·016; 64·2	−0·000	−0·440, 0·439	−0·078	−0·329, 0·172	< 0·001
EPA and DHA	5/350	0·000; 93·9	0·702	−0·310, 1·714	0·458	0·234, 0·682	
n-3 PUFA	8/355	0·000; 86·4	0·642	0·034, 1·250	0·638	0·416, 0·860	
Administration routes							
Oral	7/361	0·000; 77·1	0·330	−0·151, 0·811	0·445	0·232, 0·658	0·063
Nasal feeding	10/543	0·000; 92·2	0·478	−0·176, 1·133	0·263	0·084, 0·442	
Intravenous	2/55	0·056; 72·6	1·266	−0·132, 2·664	0·929	0·358, 1·500	
Therapy duration (month)							
≤ 1	12/601	0·000; 91·0	0·614	0·029, 1·198	0·332	0·161, 0·502	0·472
> 1	7/358	0·000; 78·2	0·302	−0·195, 0·798	0·432	0·218, 0·646	
Primary concurrent treatment							
Chemotherapy	4/224	0·004; 77·9	0·606	−0·101, 1·312	0·737	0·461, 1·012	0·004
Postoperation	10/480	0·000; 92·2	0·706	−0·013, 1·425	0·349	0·156, 0·543	
Others	5/255	0·054; 57·0	0·066	−0·319, 0·451	0·108	−0·140, 0·356	
Age of patients (years)							
≤ 60	14/659	0·000; 87·7	0·600	0·123, 1·076	0·355	0·194, 0·516	0·079
> 60	4/160	0·000; 90·9	0·000	−1·096, 1·097	0·027	−0·301, 0·355	
NR	1/140		0·823	0·478, 1·168	0·823	0·478, 1·168	

SMD, standardised mean difference; DB, double-blind; NR, not reported.

Substantial differences between the anti-inflammatory effects of EPA and DHA were found[74]. The use of DHA alone was not reported in the included articles. A borderline result was observed for EPA use alone in IL-6. Alternatively, a substantial impact of TNF was observed. Subgroup analysis suggested that the combination of EPA and DHA have higher benefits than EPA alone. However, a recent network meta-analysis[75] and a head-to-head comparison study[76] did not find remarkable differences in IL-6 and TNF levels between DHA and EPA. Results of *in vitro* studies were mixed[57,61,77,78]. Some were suggestive of more potent in EPA[57,79], whereas others showed different results[61,77]. Additionally, no remarkable differences in some inflammation-related genes expressing in human immune cells were found between the effects of EPA and DHA[80]. Thus, whether EPA or DHA is superior to the other in terms of anti-inflammatory activity remains unclear.

Therapy or administrative duration may be one vital factor influencing the anti-inflammatory properties of *n*-3 PUFA. Previous data seemed to support significant decrease in IL-6 and TNF levels from longer duration of therapy[25,41,81].

Inconsistent findings were provided by current subgroup analyses. A significant decrease in TNF was observed after long-term therapy, whereas a significant decrease in IL-6 was observed after short-term therapy. The optimal duration of *n*-3 PUFA was poorly determined and may have been influenced by multiple factors. Among the most critical factors, particular attention should be paid to the anti-inflammatory pathways of *n*-3 PUFA. Incorporation into cell membrane phospholipids can rapidly modify cell function, and 26 weeks are needed to alter the gene expression profiles to anti-inflammatory status in human blood mononuclear cells[82]. Additionally, *n*-3 PUFA can act directly on inflammatory cells by decreasing inflammatory cytokine production through the activation of free fatty acid receptors 1 and 4[83] and enzymatically produce specialised pro-resolving mediators to orchestrate the resolution of inflammation[84]. The precise anti-inflammatory pathways of *n*-3 PUFA are complex[6,8] and vary under various conditions, including doses and proportions[85]. Thus, varying the duration of *n*-3 PUFA administration for the desired effects is conceivable.

Table 3. The results of meta-regression analyses

	IL-6		TNF	
Variable	No. study/patient	P	No. study/patient	P
Publication year	19/859	0·058	15/810	0·701
Study design	19/859	0·633	15/810	0·940
Jadad score	19/859	0·832	15/810	0·511
Sample size	19/859	0·864	15/810	0·708
Study area	19/859	0·346	15/810	0·684
Fatty acid types	19/859	0·297	15/810	0·134
Administration routes	19/859	0·930	15/810	0·745
Therapy duration	19/859	0·221	15/810	0·281
Primary concurrent treatment	19/859	0·639	15/810	0·222
Basic inflammatory factor levels	18/842	0·248	15/810	0·146
Age	19/859	0·511	15/810	0·674
BMI	11/574	0·536	NS	NS

NS, no statistics.

Table 4. The results of subgroup analyses for TNF

			Random effects		Fixed effects		
Subgroup	No. of study/patient	Heterogeneity P; I^2 (%)	SMD	95 % CI	SMD	95 % CI	$P_{subgroup}$
Design							
DB	7/466	0·000; 77·9	0·724	0·293, 1·154	0·606	0·417, 0·795	0·646
Non-DB	8/344	0·129; 37·6	0·707	0·421, 0·993	0·674	0·454, 0·894	
Sample size							
≤ 40	5/147	0·164; 38·6	1·149	0·684, 1·615	1·125	0·771, 1·479	0·003
> 40	10/663	0·164; 38·6	0·559	0·298, 0·820	0·539	0·383, 0·696	
Jadad score							
≤ 3	6/219	0·548; 0·0	1·081	0·795, 1·368	1·081	0·795, 1·368	< 0·001
≥ 4	9/591	0·005; 63·9	0·518	0·228, 0·807	0·486	0·321, 0·652	
Study area							
America	4/183	0·186; 37·7	0·569	0·169, 0·969	0·527	0·230, 0·825	0·156
Asia	7/478	0·052; 52·0	0·834	0·547, 1·121	0·749	0·562, 0·936	
Europe	4/149	0·001; 82·9	0·606	−0·234, 1·446	0·406	0·070, 0·742	
Cancer sites							
Head and neck	3/143	0·197; 38·4	0·108	−0·340, 0·556	0·100	−0·243, 0·442	0·003
Gastric	4/273	0·093; 53·3	0·816	0·434, 1·198	0·733	0·486, 0·981	
Colorectal	4/232	0·581; 0·0	0·630	0·365, 0·894	0·630	0·365, 0·894	
Others	4/172	0·004; 77·4	1·109	0·408, 1·809	0·952	0·629, 1·276	
Fatty acid types							
EPA	3/161	0·215; 34·9	0·400	0·009, 0·792	0·383	0·069, 0·696	0·186
EPA and DHA	5/244	0·004; 74·0	1·001	0·491, 1·510	0·738	0·517, 0·960	
n-3 PUFA	7/305	0·010; 64·3	0·677	0·280, 1·073	0·660	0·426, 0·895	
Administration routes							
Oral	6/291	0·072; 50·5	0·903	0·509, 1·297	0·772	0·531, 1·013	0·157
Nasal feeding	7/414	0·001; 74·2	0·693	0·284, 1·101	0·637	0·436, 0·838	
Intravenous	1/41		0·487	−0·135, 1·109	0·487	−0·135, 1·109	
Other	1/64		0·150	−0·341, 0·640	0·150	−0·341, 0·640	
Therapy duration (month)							
≤ 1	9/484	0·003; 66·0	0·656	0·328, 0·983	0·620	0·434, 0·805	0·796
> 1	6/326	0·010; 66·7	0·823	0·380, 1·267	0·658	0·432, 0·884	
Primary concurrent treatment							
Chemotherapy	4/218	0·001; 70·2	1·075	0·425, 1·725	0·785	0·506, 1·065	0·339
Postoperation	8/416	0·021; 69·3	0·670	0·291, 1·050	0·628	0·427, 0·828	
Others	3/176	0·200; 37·8	0·492	0·107, 0·878	0·478	0·176, 0·779	
Age of patients (years)							
≤ 60	12/586	0·003; 61·1	0·808	0·522, 1·093	0·711	0·542, 0·881	0·160
> 60	2/84	0·010; 85·0	0·267	−0·866, 1·400	0·271	−0·168, 0·710	
NR	1/140		0·549	0·211, 0·886	0·549	0·211, 0·886	

SMD, standardized mean difference; DB, double-blind; NR, not reported.
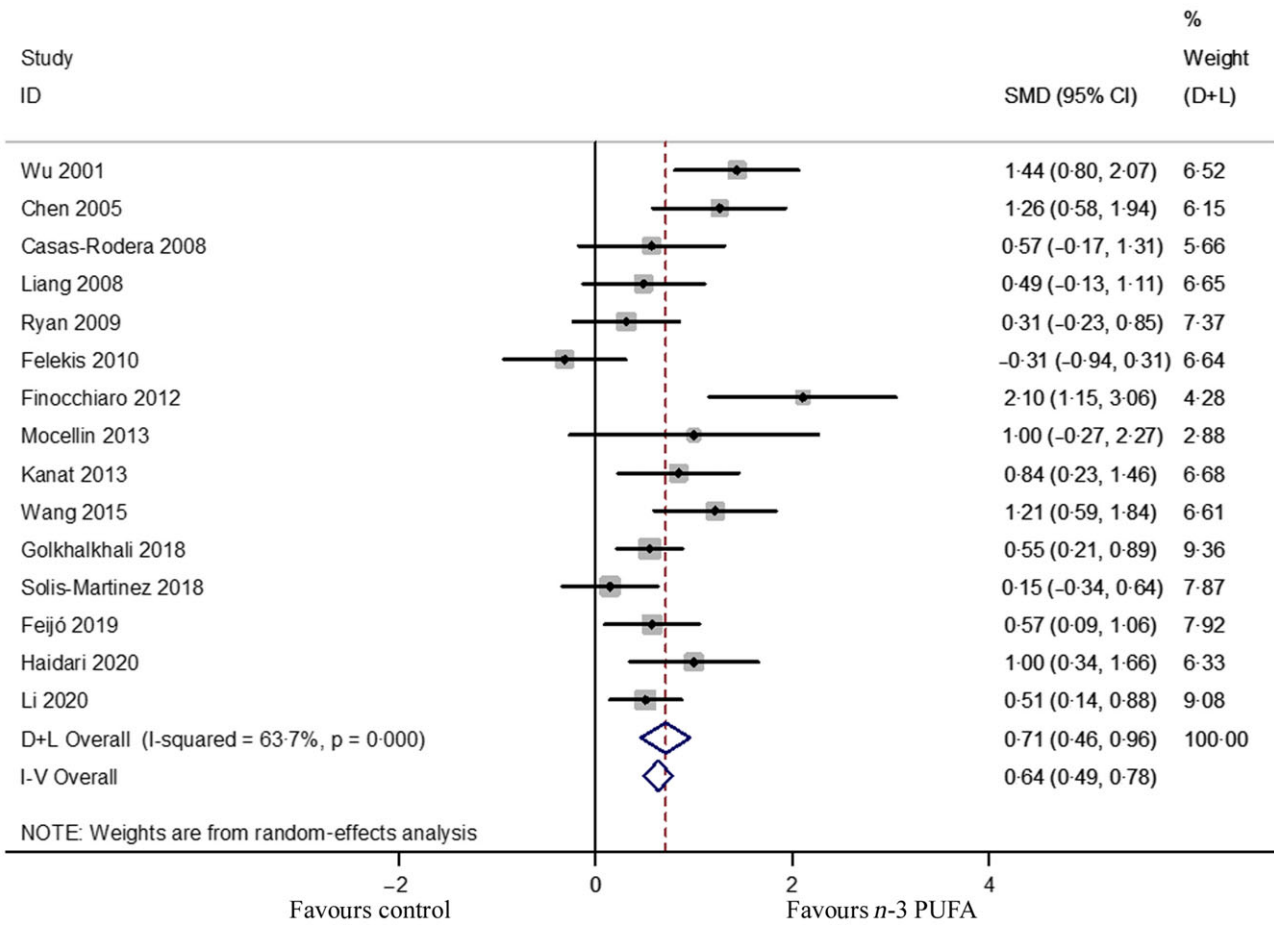
Y. Guo *et al.*

Fig. 3. Meta-analysis of *n*-3 PUFA administration on TNF in cancer patients. CI, confidence interval; SMD, standardized mean difference.
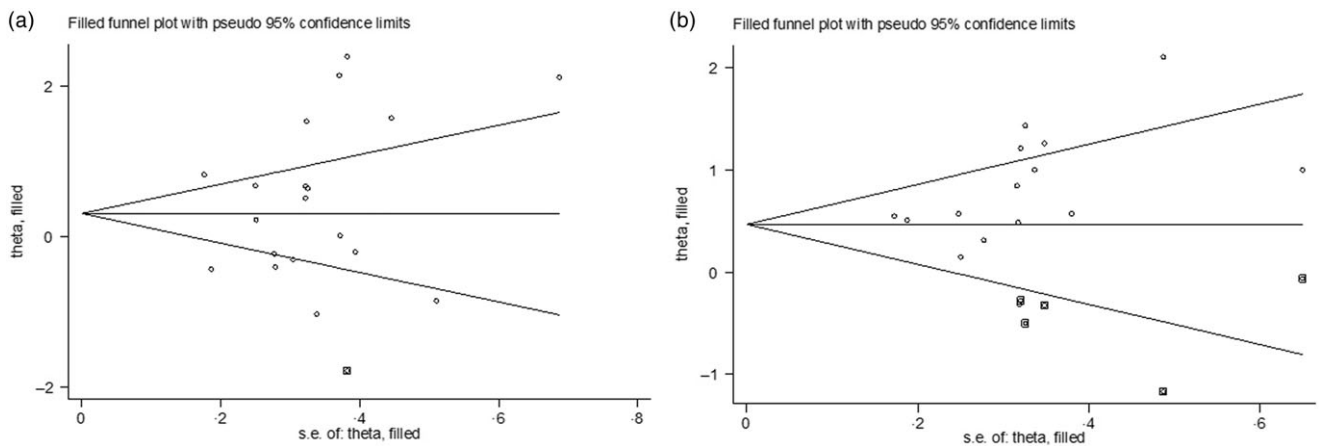

Fig. 4. The filled funnel plot for IL-6 (a) and TNF (b). Open circles are for original data, and solid squares are for imputed "filled" values.

Doses and proportions are the other two fundamental factors influencing the anti-inflammatory properties of *n*-3 PUFA[7,86]. The optimal doses have not yet been firmly established[8]. Different inflammatory conditions possibly require different doses[87]. The threshold[88] and dose–response relationship within a certain range[89,90] of *n*-3 PUFA administration have

been reported. However, the dose–response relationship and diverse effects of different proportions of *n*-3 PUFA have not been analysed because of limited data.

Additionally, differences in administration routes, primary concurrent treatment, basic inflammatory factor levels and patient age cannot independently predict the effectiveness of

n-3 PUFA administration on IL-6 and TNF levels according to the results of subgroup and meta-regression analyses.

Some limitations should be noted when interpreting the findings of this meta-analysis. Firstly, the number of patients and studies is small, and thus are prone to selection and publication biases. Secondly, substantial variations on potential confounders were present, such as patient enrolment, cancer site, *n*-3 PUFA types and dosage, and therapy duration. Thirdly, the subgroup results were defined *post hoc*, and the means of the studies instead of individual patient's data were used as data points. Finally, the means and standard deviations in some studies were extracted through figures or calculated from data with non-normal distribution. These limitations may have reduced the statistical power, leading to false or spurious results.

Despite that the optimal regimens using *n*-3 PUFA were not identified, the present result supports the use of *n*-3 PUFA for patients with cancer, possibly excluding head and neck cancer, because of their anti-inflammatory properties. More benefits were observed in Asian, EPA and DHA combined, independent of administration routes, therapy duration and primary concurrent treatment. Further studies are needed to determine optimal patients and regimens that will highly benefit from the use of *n*-3 PUFA.

Acknowledgements

References

1. Greten FR & Grivennikov SI (2019) Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity* **51**, 27–41.
2. Mantovani A, Allavena P, Sica A, *et al.* (2008) Cancer-related inflammation. *Nature* **454**, 436–444.
3. Crusz SM & Balkwill FR (2015) Inflammation and cancer: advances and new agents. *Nat Rev Clin Oncol* **12**, 584–596.
4. Diakos CI, Charles KA, Mcmillan DC, *et al.* (2014) Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* **15**, e493–e503.
5. Hou J, Karin M & Sun B (2021) Targeting cancer-promoting inflammation – have anti-inflammatory therapies come of age? *Nat Rev Clin Oncol* **18**, 261–279.
6. Djuricic I & Calder PC (2021) Beneficial outcomes of *n*-6 and *n*-3 polyunsaturated fatty acids on human health: an update for 2021. *Nutrients* **13**, 2421.
7. Zárate R, Jaber Vazdekis N, Tejera N, *et al.* (2017) Significance of long chain polyunsaturated fatty acids in human health. *Clin Transl Med* **6**, 25.
8. Calder PC (2018) Very long-chain *n*-3 fatty acids and human health: fact, fiction and the future. *Proc Nutr Soc* **77**, 52–72.
9. Nabavi SF, Bilotto S, Russo GL, *et al.* (2015) *n*-3 polyunsaturated fatty acids and cancer: lessons learned from clinical trials. *Cancer Metastasis Rev* **34**, 359–380.
10. D'Archivio M, Scazzocchio B, Vari R, *et al.* (2018) Recent evidence on the role of dietary pufas in cancer development and prevention. *Curr Med Chem* **25**, 1818–1836.
11. Muscaritoli M, Arends J, Bachmann P, *et al.* (2021) ESPEN practical guideline: clinical Nutrition in cancer. *Clin Nutr* **40**, 2898–2913.
12. Yates CM, Calder PC & Ed RG (2014) Pharmacology and therapeutics of *n*-3 polyunsaturated fatty acids in chronic inflammatory disease. *Pharmacol Ther* **141**, 272–282.
13. Lan T, Chen L & Wei X (2021) Inflammatory cytokines in cancer: comprehensive understanding and clinical progress in gene therapy. *Cells,* **10**, 100.
14. Grivennikov SI & Karin M (2011) Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Ann Rheum Dis* 70, i104–i108.
15. Mocellin MC, Camargo CQ, Nunes EA, *et al.* (2016) A systematic review and meta-analysis of the *n*-3 polyunsaturated fatty acids effects on inflammatory markers in colorectal cancer. *Clin Nutr* **35**, 359–369.
16. Mocellin MC, Fernandes R, Chagas TR, *et al.* (2018) A meta-analysis of *n*-3 polyunsaturated fatty acids effects on circulating acute-phase protein and cytokines in gastric cancer. *Clin Nutr* **37**, 840–850.
17. Yu J, Liu L, Zhang Y, *et al.* (2017) Effects of *n*-3 fatty acids on patients undergoing surgery for gastrointestinal malignancy: a systematic review and meta-analysis. *BMC Cancer* **17**, 271.
18. Zhao Y & Wang C (2018) Effect of *n*-3 polyunsaturated fatty acid-supplemented parenteral nutrition on inflammatory and immune function in postoperative patients with gastrointestinal malignancy: a meta-analysis of randomized control trials in China. *Medicine* **97**, e472.
19. Yan S, Li M, Yang D, *et al.* (2020) Associations between *n*-3 fatty acid supplementation and anti-inflammatory effects in patients with digestive system cancer: a meta-analysis. *Nutr Cancer* **72**, 1098–1114.
20. Pan L, Zhou Y, Yin H, *et al.* (2021) *n*-3 polyunsaturated fatty acids can reduce C-reactive protein in patients with cancer: a systematic review and meta-analysis of randomized controlled trials. *Nutr Cancer* 1–12. doi: 10.1080/01635581.2021.1931365
21. Liberati A, Altman DG, Tetzlaff J, *et al.* (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* **339**, b2700.
22. Hozo SP, Djulbegovic B & Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* **5**, 13.
23. Jadad AR, Moore RA, Carroll D, *et al.* (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* **17**, 1–12.
24. Kjaergard LL, Villumsen J & Gluud C (2001) Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* **135**, 982–989.
25. Sunpaweravong S, Puttawibul P, Ruangsin S, *et al.* (2013) Randomized study of antiinflammatory and immune-modulatory effects of enteral immunonutrition during concurrent chemoradiotherapy for esophageal cancer. *Nutr Cancer* **66**, 1–5.
26. Bakker N, van den Helder RS, Stoutjesdijk E, *et al.* (2020) Effects of perioperative intravenous ω-3 fatty acids in colon cancer patients: a randomized, double-blind, placebo-controlled clinical trial. *Am J Clin Nutr* **111**, 385–395.
27. Turnock A, Calder PC, West AL, *et al.* (2013) Perioperative immunonutrition in well-nourished patients undergoing

British Journal of Nutrition

28. Gogos CA, Ginopoulos P, Salsa B, *et al.* (1998) Dietary *n*-3 poly-unsaturated fatty acids plus vitamin E restore immuno-deficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. *Cancer* **82**, 395–402.

29. Lu Y, Chen RG, Wei SZ, *et al.* (2018) Effect of *n* 3 fatty acids on C-reactive protein and interleukin-6 in patients with advanced nonsmall cell lung cancer. *Medicine* **97**, e11971.

30. Wigmore SJ, Fearon KC, Maingay JP, *et al.* (1997) Down-regu-lation of the acute-phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is medi-ated via suppression of interleukin-6. *Clin Sci* **92**, 215–221.

31. Martinez N, Herrera M, Frias L, *et al.* (2019) A combination of hydroxytyrosol, *n*-3 fatty acids and curcumin improves pain and inflammation among early stage breast cancer patients receiving adjuvant hormonal therapy: results of a pilot study. *Clin Transl Oncol* **21**, 489–498.

32. Mohammadzadeh M, Faramarzi E, Mahdavi R, *et al.* (2013) Effect of conjugated linoleic acid supplementation on inflam-matory factors and matrix metalloproteinase enzymes in rectal cancer patients undergoing chemoradiotherapy. *Integr Cancer Ther* **12**, 496–502.

33. Mcdonald C, Bauer J, Capra S, *et al.* (2014) The muscle mass, *n*-3, diet, exercise and lifestyle (MODEL) study – a randomised controlled trial for women who have completed breast cancer treatment. *BMC Cancer* **14**, 264.

34. Gianotti L, Braga M, Fortis C, *et al.* (1999) A prospective, ran-domized clinical trial on perioperative feeding with an argi-nine-, *n*-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. *JPEN J Parenter Enteral Nutr* **23**, 314–320.

35. Furukawa K, Tashiro T, Yamamori H, *et al.* (1999) Effects of soybean oil emulsion and eicosapentaenoic acid on stress response and immune function after a severely stressful oper-ation. *Ann Surg* **229**, 255–261.

36. Wu GH, Zhang YW & Wu ZH (2001) Modulation of postoper-ative immune and inflammatory response by immune-enhanc-ing enteral diet in gastrointestinal cancer patients. *World J Gastroenterol* **7**, 357–362.

37. Chen DW, Wei FZ, Zhang YC, *et al.* (2005) Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery. *Asian J Surg* **28**, 121–124.

38. Casas-Rodera P, Gómez-Candela C, Benítez S, *et al.* (2008) Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomized clinical trial. *Nutr Hosp* **23**, 105–110.

39. Felekis D, Eleftheriadou A, Papadakos G, *et al.* (2010) Effect of perioperative immuno-enhanced enteral nutrition on inflam-matory response, nutritional status, and outcomes in head and neck cancer patients undergoing major surgery. *Nutr Cancer* **62**, 1105–1112.

40. Liang B, Wang S, Ye YJ, *et al.* (2008) Impact of postoperative *n*-3 fatty acid-supplemented parenteral nutrition on clinical out-comes and immunomodulations in colorectal cancer patients. *World J Gastroenterol* **14**, 2434–2439.

41. Ryan AM, Reynolds JV, Healy L, *et al.* (2009) Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann Surg* **249**, 355–363.

42. Silva JA, Trindade EB, Fabre ME, *et al.* (2012) Fish oil supple-ment alters markers of inflammatory and nutritional status in colorectal cancer patients. *Nutr Cancer* **64**, 267–273.

43. Kanat O, Cubukcu E, Avci N, *et al.* (2013) Comparison of three different treatment modalities in the management of cancer cachexia. *Tumori* **99**, 229–233.

44. Finocchiaro C, Segre O, Fadda M, *et al.* (2012) Effect of *n*-3 fatty acids on patients with advanced lung cancer: a double-blind, placebo-controlled study. *Br J Nutr* **108**, 327–333.

45. Roca-Rodriguez MM, Garcia-Almeida JM, Lupianez-Perez Y, *et al.* (2014) Effect of a specific supplement enriched with *n*-3 polyunsaturated fatty acids on markers of inflammation, oxidative stress and metabolic status of ear, nose and throat cancer patients. *Oncol Rep* **31**, 405–414.

46. Wang D, Zhang H, Zhang Y, *et al.* (2015) Effects of *n*-3 poly-unsaturated fatty acids on postoperative inflammatory reaction and clinical efficacy. *Zhonghua Wei Chang Wai Ke Za Zhi* **18**, 651–655.

47. Carvalho TC, Cruz BC, Viana MS, *et al.* (2017) Effect of nutri-tional supplementation enriched with eicosapentaenoic acid on inflammatory profile of patients with oral cavity cancer in antineoplastic pretreatment: a controlled and randomized clini-cal trial. *Nutr Cancer* **69**, 428–435.

48. Golkhalkhali B, Rajandram R, Paliany AS, *et al.* (2018) Strain-specific probiotic (microbial cell preparation) and *n*-3 fatty acid in modulating quality of life and inflammatory markers in colo-rectal cancer patients: a randomized controlled trial. *Asia Pac J Clin Oncol* **14**, 179–191.

49. Solis-Martinez O, Plasa-Carvalho V, Phillips-Sixtos G, *et al.* (2018) Effect of eicosapentaenoic acid on body composition and inflammation markers in patients with head and neck squ-amous cell cancer from a public hospital in mexico. *Nutr Cancer* **70**, 663–670.

50. Feijó PM, Rodrigues VD, Viana MS, *et al.* (2019) Effects of ω-3 supplementation on the nutritional status, immune, and inflam-matory profiles of gastric cancer patients: a randomized con-trolled trial. *Nutrition* **61**, 125–131.

51. Li K, Xu Y, Hu Y, *et al.* (2020) Effect of enteral immunonutrition on immune, inflammatory markers and nutritional status in gas-tric cancer patients undergoing gastrectomy: a randomized double-blinded controlled trial. *J Invest Surg* **33**, 950–959.

52. Haidari F, Abiri B, Iravani M, *et al.* (2020) Randomized study of the effect of vitamin D and *n*-3 fatty acids cosupplementation as adjuvant chemotherapy on inflammation and nutritional status in colorectal cancer patients. *J Dietary Supplement* **17**, 384–400.

53. Mocellin MC, Pastore ESJA, Camargo CQ, *et al.* (2013) Fish oil decreases C-reactive protein/albumin ratio improving nutri-tional prognosis and plasma fatty acid profile in colorectal cancer patients. *Lipids* **48**, 879–888.

54. Cerchietti LC, Navigante AH & Castro MA (2007) Effects of eico-sapentaenoic and docosahexaenoic *n*-3 fatty acids from fish oil and preferential Cox-2 inhibition on systemic syndromes in patients with advanced lung cancer. *Nutr Cancer* **59**, 14–20.

55. Read JA, Beale PJ, Volker DH, *et al.* (2007) Nutrition interven-tion using an eicosapentaenoic acid (EPA)-containing supple-ment in patients with advanced colorectal cancer. Effects on nutritional and inflammatory status: a phase II trial. *Support Care Cancer* **15**, 301–307.

56. Alfano CM, Imayama I, Neuhouser ML, *et al.* (2012) Fatigue, inflammation, and *n*-3 and *n*-6 fatty acid intake among breast cancer survivors. *J Clin Oncol* **30**, 1280–1287.

57. Khalfoun B, Thibault F, Watier H, *et al.* (1997) Docosahexaenoic and eicosapentaenoic acids inhibit *in vitro* human endothelial cell production of interleukin-6. *Adv Exp Med Biol* **400B**, 589–597.

58. Endres S, Ghorbani R, Kelley VE, *et al.* (1989) The effect of dietary supplementation with *n*-3 polyunsaturated fatty acids

on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med* **320**, 265–271.

59. Trebble T, Arden NK, Stroud MA, *et al.* (2003) Inhibition of tumour necrosis factor-α and interleukin 6 production by mononuclear cells following dietary fish-oil supplementation in healthy men and response to antioxidant co-supplementation. *Br J Nutr* **90**, 405–412.

60. Feng J, Wang Q, Yang W, *et al.* (2021) *n*-3 polyunsaturated fatty acids ameliorated inflammatory response of mammary epithelial cells and mammary gland induced by lipopolysaccharide. *Acta Biochim Biophys Sin* **53**, 1142–1153.

61. Jaudszus A, Gruen M, Watzl B, *et al.* (2013) Evaluation of suppressive and pro-resolving effects of EPA and DHA in human primary monocytes and T-helper cells. *J Lipid Res* **54**, 923–935.

62. Rodriguez-Vita J & Lawrence T (2010) The resolution of inflammation and cancer. *Cytokine Growth Factor Rev* **21**, 61–65.

63. Jones SA & Jenkins BJ (2018) Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. *Nat Rev Immunol* **18**, 773–789.

64. Lacina L, Brabek J, Kral V, *et al.* (2019) Interleukin-6: a molecule with complex biological impact in cancer. *Histol Histopathol* **34**, 125–136.

65. Lebrec H, Ponce R, Preston BD, *et al.* (2015) Tumor necrosis factor, tumor necrosis factor inhibition, and cancer risk. *Curr Med Res Opin* **31**, 557–574.

66. Szlosarek P, Charles KA & Balkwill FR (2006) Tumour necrosis factor-α as a tumour promoter. *Eur J Cancer* **42**, 745–750.

67. Grenade C, Phelps MA & Villalona-Calero MA (2014) Race and ethnicity in cancer therapy: what have we learned? *Clin Pharmacol Ther* **95**, 403–412.

68. Shavers VL & Brown ML (2002) Racial and ethnic disparities in the receipt of cancer treatment. *J Natl Cancer Inst* **94**, 334–357.

69. Stowe RP, Peek MK, Cutchin MP, *et al.* (2010) Plasma cytokine levels in a population-based study: relation to age and ethnicity. *J Gerontol A Biol Sci Med Sci* **65**, 429–433.

70. Sekikawa A, Steingrimsdottir L, Ueshima H, *et al.* (2012) Serum levels of marine-derived *n*-3 fatty acids in Icelanders, Japanese, Koreans, and Americans-a descriptive epidemiologic study. *Prostaglandins Leukot Essent Fatty Acid* **87**, 11–16.

71. Toiyama Y, Fujikawa H, Koike Y, *et al.* (2013) Evaluation of preoperative C-reactive protein aids in predicting poor survival in patients with curative colorectal cancer with poor lymph node assessment. *Oncol Lett* **5**, 1881–1888.

72. Guo YZ, Pan L, Du CJ, *et al.* (2013) Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. *Asian Pac J Cancer Prev* **14**, 243–248.

73. Bonomi M, Patsias A, Posner M, *et al.* (2014) The role of inflammation in head and neck cancer. *Adv Exp Med Biol* **816**, 107–127.

74. Gorjao R, Azevedo-Martins AK, Rodrigues HG, *et al.* (2009) Comparative effects of DHA and EPA on cell function. *Pharmacol Ther* **122**, 56–64.

75. Vors C, Allaire J, Mejia SB, *et al.* (2021) Comparing the effects of docosahexaenoic and eicosapentaenoic acids on inflammation markers using pairwise and network meta-analyses of randomized controlled trials. *Adv Nutr* **12**, 128–140.

76. Allaire J, Couture P, Leclerc M, *et al.* (2016) A randomized, crossover, head-to-head comparison of eicosapentaenoic acid and docosahexaenoic acid supplementation to reduce inflammation markers in men and women: the Comparing EPA to DHA (ComparED) Study. *Am J Clin Nutr* **104**, 280–287.

77. Weldon SM, Mullen AC, Loscher CE, *et al.* (2007) Docosahexaenoic acid induces an anti-inflammatory profile in lipopolysaccharide-stimulated human THP-1 macrophages more effectively than eicosapentaenoic acid. *J Nutr Biochem* **18**, 250–258.

78. So J, Wu D, Lichtenstein AH, *et al.* (2021) EPA and DHA differentially modulate monocyte inflammatory response in subjects with chronic inflammation in part via plasma specialized pro-resolving lipid mediators: a randomized, double-blind, crossover study. *Atherosclerosis* **316**, 90–98.

79. Sierra S, Lara-Villoslada F, Comalada M, *et al.* (2008) Dietary eicosapentaenoic acid and docosahexaenoic acid equally incorporate as docosahexaenoic acid but differ in inflammatory effects. *Nutr* **24**, 245–254.

80. Vors C, Allaire J, Marin J, *et al.* (2017) Inflammatory gene expression in whole blood cells after EPA vs. DHA supplementation: results from the ComparED study. *Atherosclerosis* **257**, 116–122.

81. Hershman DL, Unger JM, Crew KD, *et al.* (2015) Randomized multicenter placebo-controlled trial of *n*-3 fatty acids for the control of aromatase inhibitor-induced musculoskeletal pain: SWOG S0927. *J Clin Oncol* **33**, 1910–1917.

82. Bouwens M, van de Rest O, Dellschaft N, *et al.* (2009) Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. *Am J Clin Nutr* **90**, 415–424.

83. Kimura I, Ichimura A, Ohue-Kitano R, *et al.* (2020) Free fatty acid receptors in health and disease. *Physiol Rev* **100**, 171–210.

84. Basil MC & Levy BD (2016) Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. *Nat Rev Immunol* **16**, 51–67.

85. Katan MB, Deslypere JP, van Birgelen AP, *et al.* (1997) Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. *J Lipid Res* **38**, 2012–2022.

86. Dasilva G, Pazos M, Garcia-Egido E, *et al.* (2015) Healthy effect of different proportions of marine *n*-3 PUFAs EPA and DHA supplementation in Wistar rats: lipidomic biomarkers of oxidative stress and inflammation. *J Nutr Biochem* **26**, 1385–1392.

87. Calder PC, Albers R, Antoine JM, *et al.* (2009) Inflammatory disease processes and interactions with nutrition. *Br J Nutr* 101, S1–S45.

88. Kew S, Banerjee T, Minihane AM, *et al.* (2003) Lack of effect of foods enriched with plant- or marine-derived *n*-3 fatty acids on human immune function. *Am J Clin Nutr* **77**, 1287–1295.

89. Ras RT, Demonty I, Zebregs YE, *et al.* (2014) Low doses of eicosapentaenoic acid and docosahexaenoic acid from fish oil dose-dependently decrease serum triglyceride concentrations in the presence of plant sterols in hypercholesterolemic men and women. *J Nutr* **144**, 1564–1570.

90. Flock MR, Skulas-Ray AC, Harris WS, *et al.* (2013) Determinants of erythrocyte *n*-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. *J Am Heart Assoc* **2**, e513.