nutrients

MDPI

Systematic Literatures Review

N-3 Fatty Acids Improve Treatment Efficacy and Survival in Cancer?

Catarina Oliveira[1]*, Pedro Miguel Neves[1], Teresa Santos[1,2,3], Luís Manuel Capelas[4] and Paula Ravasco [1,5,6,]

[1] Universidade Católica Portuguesa, Centre for Interdisciplinary Research in Health (CIIS); catarinasoaresdeoliveiramail.com
[2] Universidade Europeia, Lisboa
[3] Faculdade de Medicina, Instituto de Saúde Ambiental, Universidade de Lisboa, Portugal
[4] Universidade Católica Portuguesa, Institute of Health Sciences, Centre for Interdisciplinary Research in Health (CIIS)
[5] University Hospitalar of Santa Maria
[6] University of Lisbon

* Correspondence: catarinasoaresdeoliveira@gmail.com;

Received: date; Accepted: date; Published: date

It is suggested that long chain n-3 polyunsaturated fatty acids (PUFA) play a promising role as an adjuvant to oncologic treatments. Therefore, we aimed to explore the impact of PUFA supplementation on improving treatment efficacy, disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS). A systematic review of published literature was conducted on PubMed. Experimental and observational human studies were selected and some studies were added trough manual research of previous quoted bibliography. Sixteen studies conducted in cancer patients (breast, colorectal, stomach, pancreatic, lung or leukaemia/lymphoma) were included. Seven studies showed positive clinical outcomes, i.e. weight stabilisation and/or gain of lost weight, improved nutritional status, increased energy-protein intake and improved quality of life (QoL). Also, eight studies, showed improved, time to progression, DFS, PFS, and OS. Additionally, one study revealed a higher treatment tolerance and increased 1-year-OS. In conclusion, n-3 PUFAs intake, improved clinical outcomes, QoL, treatment efficacy and survival in patients with breast, colorectal, stomach, pancreatic and lung cancer or leukaemia/lymphoma. The extraordinary potential of n-3 PUFAs as an adjuvant therapy in oncology, demands more research in order to clarify ideal dosage, intervention timing and duration, as well as the most appropriate route of administration.

Keywords: cancer**;** survival; omega-3; fatty acids; chemotherapy

1. Introduction

Cancer is among the leading causes of morbidity and is the second leading cause of death mortality worldwide and the number of new cases is expected to rise significantly over the next decade[1]. In 2018 the estimated number of new cases of cancer, worldwide, in both sexes and all ages was 18 078 957 and cancer was responsible for an estimated 9 555 027 deaths[2].

Despite major advances in cancer therapy, cancer treatment still faces challenges, among other things, due to its non-selectivity and severe side effects [3]. Cancer therapies' side effects can seriously affect physical and emotional health, quality of life and constitute a challenge to treatment tolerability and adherence, witch consequently may jeopardise treatment outcome and efficacy.

Nutrition is a key factor in oncology and throughout the whole course of cancer treatment. It can play a determinant role managing cancer related symptoms and reduce adverse side effects associated with anti-neoplastic treatment(s), probably affecting the fulfilment of treatment.

On top of that, nutrition It can influence the development of the disease and has the potential to enhance treatment efficacy and recovery and improve prognosis [4].

Besides having a wide range of physiological roles linked to certain health or clinical benefits, long chain n-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA 20:5n-3) and docosahexaenoic acid (DHA 22:6n-3), have shown their ability of protecting against a number of conditions and may even be used as a treatment [5].

EPA and DHA are synthesise from α-linolenic acid through a process of series of desaturation and elongation reactions. Humans have limited ability to synthesise EPA and DHA from α-linolenic acid, which is found in seed oils[5], and thus must be obtained from dietary sources or supplementation. Fish, in particularly oily fish like mackerel, herring, salmon, tuna, and sardines, lean fish liver (e.g. cod liver), and other sea foods are the best sources of long chain n-3 polyunsaturated fatty acids[5].

Due to their ample biological effect, n-3 PUFA are commonly employed in the nutritional therapy of cancer patients, mainly as an adjunctive treatment [6].

It is suggested that dietary intake of EPA and DHA can play an interesting role in the disease management by favourably modulate treatment responses and likely improving therapeutic outcome and therefore be a potentially useful adjuvant for antineoplastic therapy. It is recommended that, at least, 2 g/day are required for clinical benefit on nutrition-related endpoints. When supplemented, fish oil (4 - 6 g/day) and long-chain n-3 fatty acids (1 -2 g/day) are mostly well-tolerated[1].

There are multiple proposed molecular mechanisms whereby n-3 PUFA can show their potentially antineoplastic activity and inhibit the promotion and progression stages of carcinogenesis, namely anti-inflammatory, anti-proliferative, pro-apoptotic, anti-invasion, anti-metastatic and epigenetic regulation [7-10].

Also, in vitro and in vivo studies in tumor-bearing animals and in different human cancer cell line indicate that n-3 PUFA can increase tumor cells sensitivity to conventional therapies, like chemotherapy and radiation therapy[11]. Furthermore, it was recently demonstrated that EPA can activate host antitumor immunity by inhibiting tumor IDO expression, suggesting that EPA can be enormous potential for cancer immunotherapy [12].

As a result of the lipophilic nature, n-3 PUFA are promptly incorporated into the lipid bilayer of cells disrupting the membrane structure and fluidity of active cells, and thus likely to influences the chemosensitivity, especially for tumor cells [3]. Moreover, it is suggested that EPA and DHA can alter cytotoxicity and/or activity of a variety of anticancer drugs to human cancer cell lines used as models for breast (hormone sensitive and insensitive), prostate (hormone sensitive and insensitive), colon, lung, cervical, ovarian, gastric, bladder cancers, neuroblastomas, leukaemia, or lymphomas. [13]. Specifically, EPA and DHA seem to have de ability to enhance the effect of drugs used in cancer treatment, like doxorubici, epirubicin, 5-fluorouraci, mitomycin C, arabinosylcytosine, tamoxifen, and irinotecan/CPT-11[11].

Thus improving treatment efficacy against some types of tumors, especially those otherwise resistant to treatments and enhancing the uptake of anti-cancer drugs both by drug-sensitive and drug-resistant tumor cells [9,10,14,15].

Interestingly, besides selectively inducing apoptosis of tumor cells, including those that are resistant to treatment, with little or no cytotoxic effect on healthy cells [9,14,16], EPA and most specially DHA in combination with anticancer agents, have showed an optimistic behaviour in enhancing curative effects, reducing side effects, and tumor-targeting abilities in preclinical studies[3].

In addition, n-3 PUFA supplementation can ameliorate some of the secondary treatment complications and related side effects, such as cachexia [11,15]. As a matter of fact, in cancer therapy PUFA are used to suppress cancer-associated cachexia and to improve patients' quality of life[17]. It

is recommended the use of n-3 PUFA supplementation in patients with advanced cancer undergoing chemotherapy, in order to stabilize or improve appetite, food intake, lean body mass and body weight in cases of risk of weight loss or malnourished[1].

Considering the wide range of potential benefits of n-3 PUFA as a cancer therapy adjuvant, we aimed to explore the promising role of n-3 PUFA supplementation on improving treatment efficacy, disease-free survival, progression-free survival and overall survival.

2. Materials and Methods

In order to review the role of n-3 fatty acids on improving treatment efficacy and survival in cancer, a systematic review of published literature was conducted on PubMed, in May 2020, using the key-words "cancer" AND "survival" AND "omega 3" AND "fatty acids" AND "chemotherapy".

The search was conducted without restriction on publishing year or language, resulting on 231 records found. However, after limiting the search to human subjects and type of study: experimental and observational studies, 41 records were identified.

As for inclusion criteria, the screening records were selected if the studies were conducted in adult cancer patients who received EPA and/or DHA supplements or who's levels of n-3 PUFA intake throw diet was assessed, in order to analyze the effects of n-3 PUFA on cancer treatment outcomes.

Studies were excluded if n-3 PUFA supplements were used to assess the EPA and/or DHA role on cancer risk or prevention, cachexia treatment or if taken in combination with other immunonutrients or drugs.

Also, some studies were identified and added trough manual research of previous quoted bibliography.

3. Results

The 16 studies included in this review (Figure 1) were conducted in patients with breast, colorectal, stomach, pancreatic and lung cancer and leukaemia/lymphoma (Table 1).

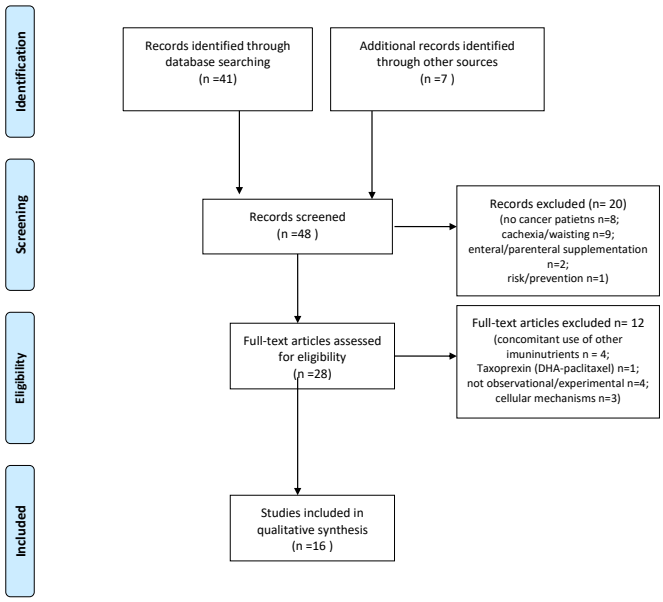

Figure 1. PRISMA flow diagram of the studies included in the review

Commented [MLC1]: Acrescentar sintaxe e critérios de inclusão e exsclusão

Commented [MLC2]: Este vai ser um pequeno problema. Só uma BD.

Commented [MLC3]: Fluxograma Prisma necessário.

While one studied was carried on breast cancer survivors and another studied was developed with colorectal with liver metastasis patients undergoing a liver resection, the other 13 studies were conducted in cancer patients undergoing chemotherapy.

In most of the studies, 12, cancer patients received EPA and/or DHA supplementation, trough oral nutrition supplements like capsules or fish oil, except in 2 studies where pancreatic cancer patients received a lipid emulsion. Whereas on 2 studies, the high levels of EPA and/or DHA assessed were obtained through diet intake.

Table 1. Characteristics of the studies

Author	Cancer	Treatment	n-3 PUFA	Type	Placebo	Outcome
Patterson et al. (2011)[18]	Breast (Survivors)	-	-	Dietary Intake	-	↓ Recurrence, ↑ Overall Survival
Bougnoux et al. (2009)[19]	Breast (with visceral metastases)	CT: Cyclophosphamide, 5-Fluorouracil, Epirubicin	1,8g DHA/d/5m	ONS	X	↑ Time to progression, ↑ Overall Survival
Ghoreishi Z et al. (2012)[20]	Breast	CT: Paclitaxel 75 mg/m2	0,2g EPA + 1,0g DHA/d/16w	ONS	Sunflower Oil	↓Treatment toxicity
Darwito et al. (2019)[21]	Breast	CT: Cyclophosphamide + Doxorubicin + 5-Fluorouracil (CAF)	1 g/d	ONS	Not specified	↑ Overall Survival, ↑Disease-free survival
Trabal et al. (2010)[22]	Colorectal	CT: 5-Fluorouracil + Oxaliplatin + Folinic acid or Capecitabin	2g EPA + 0,9g DHA/d/12w	ONS	X	↑ Body weight, ↑ QoL, No treatment interruptions due to toxicity*
Mocellin et al. (2013)[23]	Colorectal	CT: Xeloda. Oxaliplatin, 5-Fluorouracil/ Leucovorin	0,4g EPA + 0,2g DHA/d/9w	ONS	X	↓ CRP and CRP/ albumin, Weight Maintenance*
Van Blarigan et al. (2019)[24]	Colorectal	CT	-	Diet	-	↑ Progression-Free Survival
Cockbain et al. (2014)[25]	Colorectal Liver Metastasis	Liver resection surgery	2g EPA/d/4w	ONS	Capric and caprylic acid	↑ Overall Survival, ↑ Progression-Free Survival,

Bonatto et al. (2012)[26]	Stomach	CT: 5-Fluorouracil, Leucovorin	0,3g EPA + 0,4g DHA/d/8w	ONS	X	↑ weight ↑ blood polymorph nuclear cells
Arshad et al. (2013)[27]	Pancreatic	CT:Gemcitabine	200 mg/mL	Lipid emulsion	X	↑ Overall Survival, ↑Progression-Free Survival,
Arshad et al. (2015)[28]	Pancreatic	CT: Gemcitabine	200 mg/mL	Lipid emulsion	X	↑Progression-Free Survival, ↑ QoL
Murphy et al. (2011)[29]	NSCLC	CT: Carboplatin + vinorelbine or gemcitabine	2,2 g EPA + 0,2g or 0,5g DHA/d/10w	ONS or Fish Oil	X	↑ Response rates and clinical benefit ↑ 1-year survival
Sánchez-Lara et al. (2014)[30]	NSCLC	CT: Paclitaxel + cisplatin/carboplatin	2,2g EPA + 1g DHA /d/8w	ONS	X	↑ Energy + protein intake ↑FFM ↓ fatigue, loss of appetite ↓ neuropathy
Finocchiaro et al. (2012)[31]	NSCLC	CT: Cisplatin + Gemcitabine	2g EPA + 1,4 g DHA/d/66d	ONS	Olive Oil	↑ Weight ↓CRP, ↓ IL6
van der Meij et al. (2010)[32]	NSCLC	Chemoradiation Cisplatin/ Docetaxel + Bevacizumab	2g EPA + 0,9g DHA/d/5w	P/E dense ONS	Isocaloric Control Supplement	↑ Energy Intake Weight and FFM maintenance
Chagas et al. (2017)[33]	Leukaemia/ Lymphoma	CT	367 mg EPA + 243 mg DHA/d/9w	ONS	X	↑ Overall survival ↑ Number of CT cycles

Legend: CT – Chemotherapy; d – days; w- weeks; m – months, EPA – eicosapentaenoic acid; DHA – docosahexaenoic cacid; ONS – oral nutritional supplement; QoL – Quality of life; PMNC - peripheral blood mononuclear cell; FFM – Fat Free Mass NSCLC – Non Small Cell Lung Carcinoma; P/E – Protein/Energy; CRP – C Reactive Protein; CT – Chemotherapy; *Not statistically significant

3.1. Breast Cancer

Globally, female breast cancer is the second most diagnosed cancer. Among women is the most commonly diagnosed and the leading cause of cancer death.[2]

EPA and DHA role in breast cancer is widely studied,

One reason for this observation may be enhancement of at least some types of chemotherapeutic cytotoxicity, which has been reported for concomitant administration of DHA with anthracyclines.[34]

Furthermore, DHA showed a tumour-specific chemosensitiser activity in a phase II trial by substantially increasing survival in metastatic breast cancer patients, undergoing anthracycline and receiving. DHA capsules supplementation (1,8 g DHA/day/5 months).

Regarding treatment side effects, disabling and dose-limiting peripheral neuropathy, due to chemotherapy with paclitaxel, decreases the patients QoL and sometimes may force to change or even end the treatment. However, ω -3 PUFA (0,2 g EPA + 1 g DHA/day/16 weeks) seem to play a promising and effective role in reducing the incidence and severity of peripheral neuropathy.[20]

On these review we found 4 studies where EPA and DHA played a very interesting role on the treatment outcome of breast cancer patients.

EPA and DHA dietary intake, from food and supplements (the use of fish oil supplements was low, generally <5%) was associated with longer disease-free survival and overall survival in breast cancer survivors from the Women's Healthy Eating and Living (WHEL) Study. Also, women with higher intakes of EPA and DHA, from food, had an approximate 25% reduced risk of additional breast cancer events and had a dose-dependent reduced risk of all-cause mortality[18].

Even though supplementation of 1,8g DHA/day was well tolerated, with no adverse side effects and global compliance was 90%, there was a wide inter-individual disparity in DHA incorporation in plasma phospholipids in a phase II trial conducted in 25 breast cancer patients with rapidly progressing visceral metastases receiving an anthracycline-based chemotherapy. High incorporation of DHA into circulating phospholipids showed a tumour-specific chemosensitiser, displaying a potentially improvement in patients' treatment outcome associated with a significantly higher tme to progression and an almost doubled overall survival [19].

Also, a double blind placebo controlled trial showed the efficacy of n-3 PUFA supplementation, mainly DHA, as a prophylactic agent against chemotherapy induced neurotoxicity with paclitaxel, which could eventually lead to a reduction in patients' quality of life and in some cases force the oncologist to change or even end the treatment. This trial was conducted in 57 female breast cancer patients and significant difference were observed between the n-3 PUFA supplemented group and the placebo group, with the supplemented group showing a 70% lower risk of peripheral neuropathy incidence. [20].

More recently, a double-blind randomized control trial with 48 patients with locally advanced breast cancer treated with CAF neoadjuvant chemotherapy and mastectomy showed a significantly higher overall survival and progression-free survival in patients receiving a supplementation of 1 g/day of n-3 PUFA in form of an oil-fish capsule[21].

3.2. Colorectal carcinoma (CRC)

Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with 1,8 million new cases and almost 861 000 deaths in 2018[2].

The majority of evidence linking anti-CRC activity with n-3 PUFA has focussed on decreased CRC risk. However, more recently, preclinical data and human observational studies have begun to make the case for adjuvant treatment of advanced CRC.

Also, some studies show results that support need for more research regarding the potential use of n-3 PUFA as adjuvant in CRC therapy, due to different anticancer mechanisms of action in CRC cells in vitro and in vivo, without toxic effects [7,35].

The potential positive intervention of EPA ONS (1,6g EPA/day) plus dietary counselling, on chemotherapy tolerability in patients with advanced CRC was described in a small randomized control trial with 11 stage IV CRC patients under a chemotherapy regimen. Even thought, limited by

the small sample size, patients in the supplemented group significantly increased their weight and showed better scores in important domains of HR-QoL, compared to controls. Also, although not statistically significant, the supplemented group did not experience interruptions in their chemotherapy treatment compared to the control group, with more interruptions due to toxicity[22].

Another small randomized prospective controlled clinical trial with 11 patients with CRC undergoing chemotherapy showed, although not statistically significant, a preventing effect of n-3 PUFFA supplementation with fish oil capsules (0,4g EPA + 0,2g DHA/day), on weight loss, associated with disease progression and chemotherapy. Furthermore, there was a significant reduction in the production of CRP/Alb ratio in the supplemented group, pointing to an important decrease in the risk of inflammatory and nutritional complications during treatment[23].

Taking into account preclinical data suggesting that marine n-3 PUFA could inhibit the progression of CRC and in vitro studies that showed that it may improve chemotherapy efficacy in human CRC, a recently a prospective study with 1011 colon cancer patients, analysed the effects of n-3 PUFA dietary intake and described that individuals with a higher intake n-3 PUFAs had longer disease-free survival, compared to patients in lowest quartile of n-3 PUFA intake. Also, patients who consumed dark fish once a week had a 35% lower risk of cancer recurrence or death compared with those who consumed none [24].

Furthermore, a phase II double-blind, randomised, placebo-controlled trial conducted in patients with metastatic CRC, considered EPA supplementation (2g/day) safe and well-tolerated regarding patients scheduled for liver resection. EPA was well incorporated into CRC liver metastasis tissue and these patients showed a reduced tumour vascularity and benefited from prolonged postoperative overall and disease-free survival, compared with placebo[25].

3.3. Stomach Cancer

Stomach cancer is the fifth most commonly diagnosed cancer in both sexes. In males is the fourth main diagnosed cancer and the third leading cause of cancer mortality[2].

In order to investigate if supplementation with n-3 PUFA, in cancer patients receiving post-surgical tumor (mainly gastrointestinal) removal chemotherapy is able to improve the function of blood neutrophils, a randomized trial was conducted in 38 patients over 8 weeks. Patients in the control group lost an average of 2,5 kg of weight and the number of blood polymorph nuclear cells (PMNC), mainly neutrophils, and their functions (phagocytosis and hydrogen peroxide production) decreased approximately 30, 45 and 17%, respectively). On the other hand, the group receiving 2 g of fish oil with 0,3 g EPA and 0,4 g DHA/day increased body weight), PMNC number (29% increase), phagocytosis (14% increase) and superoxide production (28% increase). This maintenance of function could be important in preventing infections during this fragile time and could help to prevent tumor regrowth [26].

3.4. Pancreatic Cancer

Pancreatic cancer is one of the most fatal human cancers [36] and is a rapidly progressive disease with a poor outcome. There for, improving the efficacy of gemcitabine (considered the standard chemotherapeutic agent in the treatment of pancreatic cancer) and new preventive and therapeutic strategies are needed for improving its therapeutic outcomes [37-38].

In pancreatic cancer, the use of n-3 PUFAs could be a potential interesting chemotherapeutic strategy and an anticancer treatment adjuvant. Studies showed that both EPA and DHA have beneficial effects on pancreatic adenocarcinoma cell lines in vitro [35] and in vivo [36] resulting in a potential useful strategy to increase the therapeutic effectiveness in pancreatic cancer [37].

32 patients with advanced pancreatic cancer were enrolled in a single-arm phase II clinical trial, treated with gemcitabine (1000 mg/m^3 weekly) immediately followed by intravenous n-3 PUFA-rich lipid emulsion) for 3 weeks followed by a rest week. Its seems that n-3 PUFA supplementation lead to a high expressors of IL-6 and IL-8 which result in a significantly shorter median overall survival, compared to low expressors. In addition, high expressors of IL-8 had significantly shorter progression-free survival than low expressors [27].

Additionally, a similar single-arm phase II trial, carried on 35 pancreatic cancer patients undergoing gemcitabine immediately followed by intravenous n-3 PUFA-rich lipid emulsion treatment described a safe and feasible use of n-3 PUFFA with an increase in global health of > 10% over baseline in 47,2% of patients and more than 50% of patients had > 10% increase in QoL scores in generic symptom scores and both disease-specific domains. It was suggested a progression-free survival improvement, which is almost certainly a reflection of the improved stable disease rate [28].

3.5. Non-small cell lung cancer

Worldwide, lung cancer remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018[2]. Current treatment of advanced non-small cell lung cancer (NSCLC) is non-specific and toxic, typically consisting of platinum-based regimens such as carboplatin in combination with vinorelbine or gemcitabine.

A phase II non randomized trial conducted on 46 patients diagnosed with stage IIIB or IV NSCLC under platinum-based chemotherapy, showed that daily supplementation with n-3 PUFA gelatine capsules (2,2g EPA + 0,2g DHA) or liquid fish oil (2,2g EPA + 0,5g DHA) for 10 weeks was well tolerated and resulted in increased chemotherapy efficacy without affecting the toxicity profile. Compared with the stander of care group, patients receiving n-3 PUFA supplementation showed a greater response rate and greater clinical benefit, as a result, more patients completed all planned chemotherapy and the one-year survival tended to be greater in these patients [29].

Also, a daily supplementation of 2,2g EPA and 1g DHA seems to improve nutritional status (weight maintenance and FFM increase), as well as energy and protein intake, while decreases fatigue, loss of appetite and neuropathy in advanced NSCLC patients, undergoing chemotherapy. Contrarily to the control group that also experienced a significant increase in nausea and vomiting. Nevertheless, these randomised trial conducted in 84 patients did not establish a difference in response rate or overall survival between the groups[30].

A randomised double-blind study conducted on 33 patients with advance non-operable NSCLC, going through chemotherapy treatment, corroborate a good n-3 PUFA oral nutritional supplementation compliance and a positive effect of EPA and DHA on increasing body weight and reducing inflammatory indexes and in oxidative status [31].

In a double-blind study, 42 patients with stage III NSCLC subject to chemoradiation therapy, were randomly assigned to receive a protein-energy dense oral nutritional supplement containing 2g EPA and 0,9gDHA/day or an isocaloric control supplement. A better weight and FFM maintenance and was associated with the protein-energy dense ONS enriched with n3-PUFA[32].

3.6. Haematological malignancies

In vitro and review studies have concluded that EPA and DHA can induce apoptosis in leukaemic cell lineages.[33]

22 patients with haematological malignancies participated in a randomised trial, showing that ingesting gelatine capsules with 2 g/day of fish oil for 9 weeks, during chemotherapy treatment, allowed patients to undertake a greater number of chemotherapy cycles and improved overall survival in patients with leukaemia or lymphoma [33] .

4. Discussion

Several clinical trials showed the potential adjuvant role of n-3 PUFA on cancer therapy in patients with breast, colorectal, stomach, pancreatic and non-small cell lung cancer and haematological malignancies. High levels of EPA and/or DHA from diet intake, oral nutrition supplementation or intravenous lipid emulsion seem to have a positive effect on treatment tolerability and chemotherapy toxicity and improve cancer treatments outcomes, with little to no side effects to healthy cells.

N-3 PUFA supplementation, with in the recommended dosage (approximately 2g/day) is safe, and it seems to have a good compliance and no significant adverse side effects.

In breast cancer patients n-3 PUFA played an important role in reducing recurrence and improving time to progression, disease free survival and overall survival. Also, although, outcomes like longer disease-free survival weren't analysed, a prophylaxis effect against peripheral neuropathy was described in a study with breast cancer patients.

Additionally, some studies conducted in colorectal patients showed an improved progression-free survival and overall survival, with other studies suggesting better clinical outcomes and however, not statistically significant a better treatment adherence with no treatment interruption due to adverse treatment side effects.

Equally, n-3 PUFA also improved progression-free survival, overall survival and QoL in pancreatic cancer patients.

The positive effect on clinical outcomes was, as well, described in several studies with NSCLC patients. Particularly, one study reported and an increased 1-year overall survival.

Haematological malignancies patients exhibited the ability to undertake more chemotherapy cycles and a longer overall survival.

One study in performed in stomach cancer patients revealed better clinical outcomes and suggested a preventing role of n-3 PUFA regarding de reduction of chemotherapy-induced neutrophil number and function, outlining another potential use of n-3 PUFA and the need for more investigation.

The most common beneficial effects on clinical outcomes were weight and fat free mass maintenance and/or gain of lost weight, improved nutritional status, increased energy-protein intake, less loss of appetite and fatigue and improved QoL. These outcomes were described in seven studies, conducted in patients with colorectal, stomach, pancreatic, lung or leukaemia/lymphoma, under chemotherapy.

In conclusion, in order to better benefit from the enormous potential of n-3 PUFA adjuvant role in cancer therapy, further investigation and larger randomize clinical trials are needed in order to better understand how n-3 PUFA supplementation can be used to improved treatment efficacy and patient survival regarding different types of cancer, stages, treatment, type of supplementation, mechanisms of action, optimal dosage, timing and duration, good compliance, supplementation bioavailability and high cell incorporation ability.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript.", please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

Funding: This research received no external funding

Acknowledgments: In this section you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Arends, J.; Bachmann, P.; Baracos, V.; Barthelemy, N.; Bertz, H.; Bozzetti, F.; Fearon, K.; Hütterer, E.; Isenring, E.; Kaasa, S.; et al. ESPEN guidelines on nutrition in cancer patients. *Clin. Nutr.* **2017**, *36*, 11–48, doi:10.1016/j.clnu.2016.07.015.
2. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin.* **2018**, *68*, 394–424, doi:10.3322/caac.21492.
3. Wang, J.; Luo, T.; Li, S.; Zhao, J. The powerful applications of polyunsaturated fatty acids in improving the therapeutic efficacy of anticancer drugs. *Expert Opin. Drug Deliv.* **2012**, *9*, 1–7, doi:10.1517/17425247.2011.618183.
4. de Carvalho, G.; Camilo, M.E.; Ravasco, P. Qual a relevância da nutrição em oncologia? *Acta Med. Port.* **2011**, *24*, 1041–1050.
5. Calder, P.C. Mechanisms of Action of (n-3) Fatty Acids. *J. Nutr.* **2012**, *142*, 592S–599S, doi:10.3945/jn.111.155259.desaturase.
6. Freitas RDS, C.M. Protective E ff ects of Omega-3 Fatty Acids in Cancer-Related Complications. *Nutrients* **2019**, *11(5)*, 1–23, doi:doi:10.3390/nu11050945.
7. Eliseo, D.D.; Rocco, G. Di; Loria, R.; Soddu, S.; Santoni, A.; Velotti, F. Epitelial-to-mesenchimal transition and invasion are upmodulated by tumor- expressed granzyme B and inhibited by docosahexaenoic acid in human colorectal cancer cells. *J. Exp. Clin. Cancer Res.* **2016**, *35*, 1–11, doi:10.1186/s13046-016-0302-6.
8. Back, G. Dietary long-chain n ϫ 3 fatty acids for the prevention of cancer : a review of potential mechanisms 1 – 3. *Am. J. Clin. Nutr.* **2004**, *79*, 935–45.
9. D'Eliseo, D.; Velotti, F. Omega-3 Fatty Acids and Cancer Cell Cytotoxicity: Implications for Multi-Targeted Cancer Therapy. *J. Clin. Med.* **2016**, *5*, 15, doi:10.3390/jcm5020015.
10. Biondo, P.D.; Brindley, D.N.; Sawyer, M.B.; Field, C.J. The potential for treatment with dietary long-chain polyunsaturated n-3 fatty acids during chemotherapy. *J. Nutr. Biochem.* **2008**, *19*, 787–796, doi:10.1016/j.jnutbio.2008.02.003.
11. Corsetto, P.A.; Colombo, I.; Riganti, C. ω -3 Long Chain Polyunsaturated Fatty Acids as Sensitizing Agents and Multidrug Resistance Revertants in Cancer Therapy. *Int. J. Mol. Sci* **2017**, *18*, 2770, doi:10.3390/ijms18122770.
12. Wang, C.C.; Yang, C.J.; Wu, L.H.; Lin, H.C.; Wen, Z.H.; Lee, C.H. Eicosapentaenoic acid reduces indoleamine 2,3-dioxygenase 1 expression in tumor cells. *Int. J. Med. Sci.* **2018**, *15*, 1296–1303, doi:10.7150/ijms.27326.
13. Hajjaji, N.; Bougnoux, P. Selective sensitization of tumors to chemotherapy by marine-derived lipids : A review. *Cancer Treat. Rev.* **2013**, *39*, 473–488, doi:10.1016/j.ctrv.2012.07.001.
14. Das, U.N.; Madhavi, N. Effect of polyunsaturated fatty acids on drug-sensitive and resistant tumor cells in vitro. *Lipids Health Dis.* **2011**, *10*, 159, doi:10.1186/1476-511X-10-159.
15. Merendino, N.; Costantini, L.; Manzi, L.; Molinari, R.; D'Eliseo, D.; Velotti, F. Dietary ω -3 Polyunsaturated Fatty Acid DHA: A Potential Adjuvant in the Treatment of Cancer . *Biomed Res. Int.* **2013**, *2013*, 1–11, doi:10.1155/2013/310186.
16. Song, E.A.; Kim, H. Docosahexaenoic acid induces oxidative DNA damage and apoptosis, and enhances the chemosensitivity of cancer cells. *Int. J. Mol. Sci.* **2016**, *17*, doi:10.3390/ijms17081257.

17. Manda, K.; Kriesen, S.; Hildebrandt, G.; Fietkau, R.; Klautke, G. Omega-3 Fatty Acid Supplementation in Cancer Therapy Does Eicosapentanoic Acid Influence the Radiosensitivity of Tumor Cells ? *Strahlenther Onkol.* **2011**, *187*, 127–134, doi:10.1007/s00066-010-2166-6.
18. Patterson, R.E.; Flatt, S.W.; Newman, V.A.; Natarajan, L.; Rock, C.L.; Thomson, C.A.; Caan, B.J.; Parker, B.A.; Pierce, J.P. Marine Fatty Acid Intake Is Associated with Breast Cancer Prognosis 1 , 2. *J. Nutr. Nutr. Dis. Mar.* **2011**, *141*, 201–206, doi:10.3945/jn.110.128777.breast.
19. Bougnoux, P.; Hajjaji, N.; Ferrasson, M.N.; Giraudeau, B.; Couet, C.; Floch, O. Le Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid : a phase II trial. *Br. J. Cancer* **2009**, *101*, 1978–1985, doi:10.1038/sj.bjc.6605441.
20. Ghoreishi, Z.; Esfahani, A.; Djazayeri, A.; Djalali, M.; Golestan, B.; Ayromlou, H.; Hashemzade, S.; Jafarabadi, M.A.; Montazeri, V. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy : A randomized double-blind placebo controlled trial. *BMC Cancer* **2012**, *12*, 1–8.
21. Darwito, D.; Dharmana, E.; Riwanto, I.; Budijitno, S.; Suwardjo, S.; Purnomo, J.; Widodo, I.; Ghozali, A.; Aryandono, T.; Anwar, S.L. Effects of Omega-3 supplementation on Ki-67 and VEGF expression levels and clinical outcomes of locally advanced Breast Cancer patients treated with Neoadjuvant CAF chemotherapy: A randomized controlled trial report. *Asian Pacific J. Cancer Prev.* **2019**, *20*, 911–916, doi:10.31557/APJCP.2019.20.3.911.
22. Trabal, J.; Leyes, P.; Forga, M.; Maurel, J. Potential usefulness of an EPA-enriched nutritional supplement on chemotherapy tolerability in cancer patients without overt malnutrition. *Nutr Hosp* **2010**, *25*, 736–740, doi:10.3305/nh.2010.25.5.4616.
23. Silva, J.P.; Mocellin, M.C.; De, J.; Pastore, A.; De, C.; Camargo, Q.; De, M.E. Fish Oil Decreases C-Reactive Protein/Albumin Ratio Improving Nutritional Prognosis and Plasma Fatty Acid Profile in Colorectal Cancer Patients. *Lipids* **2013**, *48*, 879–88, doi:10.1007/s11745-013-3816-0.
24. Blarigan, E.L. Van; Fuchs, C.S.; Niedzwiecki, D.; Ye, X.; Zhang, S. Marine ω-3 Polyunsaturated Fatty Acid and Fish Intake after Colon Cancer Diagnosis and Survival: CALGB 89803 (Alliance). *Cancer Epidemiol Biomarkers Prev.* **2019**, *27*, 438–45, doi:10.1158/1055-9965.EPI-17-0689.Marine.
25. Cockbain, A.J.; Volpato, M.; Race, A.D.; Munarini, A.; Fazio, C.; Belluzzi, A.; Loadman, P.M.; Toogood, G.J.; Hull, M.A. Anticolorectal cancer activity of the omega-3 polyunsaturated fatty acid eicosapentaenoic acid. *Gut* **2014**, *063*, 1760–8, doi:10.1136/gutjnl-2013-306445.
26. Bonatto, S.J.R.; Oliveira, H.H.P.; Nunes, E.A.; Pequito, D.; Iagher, F.; Coelho, I.; Naliwaiko, K.; Kryczyk, M.; Brito, G.A.P.; Repka, J.; et al. Fish oil supplementation improves neutrophil function during Cancer chemotherapy. *Lipids* **2012**, *47*, 383–389, doi:10.1007/s11745-011-3643-0.
27. Arshad, A.; Chung, W.Y.; Steward, W.; Metcalfe, M.S.; Dennison, A.R. Reduction in circulating pro-angiogenic and pro-inflammatory factors is related to improved outcomes in patients with advanced pancreatic cancer treated with gemcitabine and intravenous omega-3 fish oil. *Hpb J.* **2013**, *15*, 428–432, doi:10.1111/hpb.12002.
28. Arshad A, Isherwood J, Mann C, Cooke J, Pollard C, Runau F, Morgan B, Steward W, Metcalfe M, D.A. Intravenous omega-3 fatty acids plus gemcitabine: potential to improve response and quality of life in advanced pancreatic Cancer. *JPEN J Parenter Enter Nutr* **2015**, *41*, 398–403, doi:https://doi.org/10.1177/0148607115595221.
29. Murphy, R.A.; Mourtzakis, M.; Chu, Q.S.C.; Baracos, V.E.; Reiman, T.; Mazurak, V.C. Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. *Cancer* **2011**, *117*, 3774–3780, doi:10.1002/cncr.25933.

30. Sánchez-Lara, K.; Turcott, J.G.; Juárez-Hernández, E.; Nuñez-Valencia, C.; Villanueva, G.; Guevara, P.; De la Torre-Vallejo, M.; Mohar, A.; Arrieta, O. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: RANDOMISED trial. *Clin. Nutr.* **2014**, *33*, 1017–1023, doi:10.1016/j.clnu.2014.03.006.
31. Finocchiaro C, Segre O, Fadda M, Monge T, Scigliano M, Schena M, et al Effect of n-3 fatty acids on patients with advanced lung cancer: a double-blind, placebo-controlled study. *Br. J. Nutr.* **2012**, *108*, 327–33, doi:10.1017/S0007114511005551.
32. van der Meij, B.S.; Langius, J.A.E.; Smit, E.F.; Spreeuwenberg, M.D.; von Blomberg, B.M.E.; Heijboer, A.C.; Paul, M.A.; van Leeuwen, P.A.M. Oral Nutritional Supplements Containing (n-3) Polyunsaturated Fatty Acids Affect the Nutritional Status of Patients with Stage III Non-Small Cell Lung Cancer during Multimodality Treatment. *J. Nutr.* **2010**, *140*, 1774–1780, doi:10.3945/jn.110.121202.
33. Chagas, T.R.; Borges, D.S.; Oliveira, P.F. De; Mocellin, M.C.; Barbosa, A.M.; Camargo, C.Q.; Moral, G. Del; Poli, A.; Calder, P.C.; Trindade, E.B.S.M.; et al. Oral fish oil positively influences nutritional-inflammatory risk in patients with haematological malignancies during chemotherapy with an impact on long-term survival : a randomised clinical trial. *J Hum Nutr Diet.* **2017**, *30*, 681–692, doi:10.1111/jhn.12471.
34. Fabian, C.J.; Kimler, B.F.; Hursting, S.D. Omega-3 fatty acids for breast cancer prevention and survivorship. *Breast Cancer Res.* **2015**, *17*, 1–11, doi:10.1186/s13058-015-0571-6.
35. A Fluckiger, A Dumont, V Derangère, C Rébé, C de Rosny, S Causse, C Thomas, L Apetoh, A Hichami, F.G.& M.R. Inhibition of colon cancer growth by docosahexaenoic acid involves autocrine production of TNFα. *Oncogene* **2016**, *35*, 4611–4622, doi:https://doi.org/10.1038/onc.2015.523.
36. Song KS, Jing K, Kim JS, Yun EJ, Shin S, Seo KS, Park JH, Heo JY, Kang JX, Suh KS, Wu T, Park JI, Kweon GR, Yoon WH, Hwang BD, L.K. Omega-3-Polyunsaturated Fatty Acids Suppress Pancreatic Cancer Cell Growth in vitro and in vivo via Downregulation of Wnt / Beta-Catenin. *Pancreatology.* **2011**, *11*, 574–584, doi:10.1159/000334468.
37. Fukui M, Sung Kang K, Okada K, T.Z.B. EPA, an Omega-3 Fatty Acid, Induces Apoptosis in Human Pancreatic Cancer Cells: Role of ROS Accumulation, Caspase-8 Activation, and Autophagy Induction. *J. Cell. Biochem.* **2013**, *114*, 192–203, doi:10.1002/jcb.24354.
38. Swamy, M. V; Citineni, B.; Patlolla, J.M.R.; Mohammed, A.; Zhang, Y.; Rao, C. V Prevention and Treatment of Pancreatic Cancer by Curcumin in Combination With Omega-3 Fatty Acids Prevention and Treatment of Pancreatic Cancer by Curcumin in Combination With Omega-3 Fatty Acids. *Nutr. Cancer* **2008**, *60*, 81–19, doi:10.1080/01635580802416703.