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REVIEW ARTICLE

## Can Omega 3 Supplements Prevent Cancer Therapy Neurocognitive Toxicity?

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Prevention

**Abstract** Therapeutics used for the treatment of cancer can generate cognitive deterioration. Any advance in the prevention of neurotoxicity would be of major importance. Omega 3, a group of polyunsaturated fatty acids, may play a prominent role in this regard. Omega 3 fatty acids exert their protective effects through multiple direct and indirect pathophysiological mechanisms. Evidence has been obtained about their use in this setting both from preclinical and clinical trials, as well as from studies on their use in other pathologies as prevalent as Alzheimer's disease and other type of dementias. This is why studies are required to confirm the hypothesis that omega 3 supplements may prevent cancer treatment-induced brain damage. ([creativecommons.org/licenses/by-nc-nd/4.0/](http://creativecommons.org/licenses/by-nc-nd/4.0/)).

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## INTRODUCTION

Cancer incidence and prevalence is considerably increasing because new therapies are able to prolong cancer patients' survival, with this adding to general population aging (with possible associated cognitive deterioration). According to the Spanish Society of Medical Oncology (SEOM), cancer incidence in Spain for 2015 was expected to be 222,069 new annual cases, with a prevalence of more than 1,500,000 patients.

On the other hand, chemotherapy and hormone therapy, as well as radiotherapy to the central nervous system, generate brain damage in the form of cognitive impairment<sup>1</sup>.

This is why correct management of neurocognitive toxicity acquires more relevance. It would be interesting to have treatments available that would help to prevent and treat this toxicity. Currently, we already have a therapeutic option available in this line: memantine, a drug approved for the treatment of Alzheimer's disease (AD) that has demonstrated efficacy in the prevention of cognitive impairment caused by whole brain irradiation of brain metastases (RTOG 0614 results)<sup>2</sup>. The likelihood to develop cognitive impairment after this type of irradiation is around 34% at six months, and it increases over time according to a recent study<sup>3</sup>. Any new evidence with regard to its prevention would be of great interest.

In this line, omega 3 fatty acids (FA) may play an important role. Omega 3 FAs are a type of polyunsaturated fatty acids (PUFA), which have this name because they are not completely saturated with hydrogen atoms and, consequently, they exhibit several carbon-carbon double bonds. They are known as omega 3 because the first double bond is located three carbons prior to the last one, the omega carbon. There are also omega 6 PUFAs and omega 9 FAs (monosaturated), with olive oil (oleic acid) being their main representative in our diet (OA, C18:1n-9) (Fig. 1).

Omega 3 FAs are derived, by the action of elongases and desaturases, from alpha-linolenic acid (ALA, C18:3n-3), and omega 6 FAs from linoleic acid (LA, C18:2n-6). These enzymes introduce new carbons into the chain and generate double bonds, respectively. Both ALA and LA are essential fatty acids, i.e. they have to be ingested in the diet since the human body is unable to synthesize them. Alpha-linolenic acid can be converted into eicosapentaenoic acid

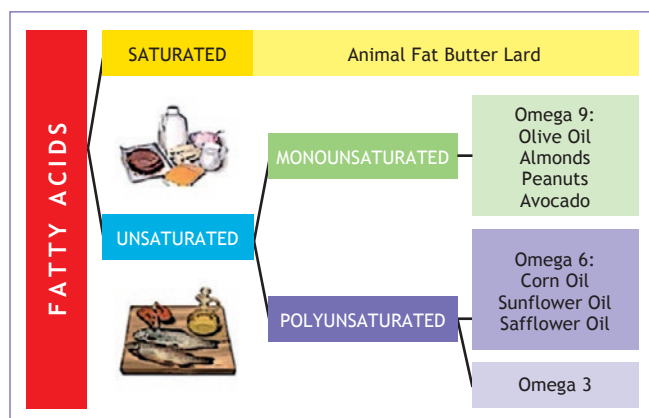


Figure 1. Types of fatty acids.

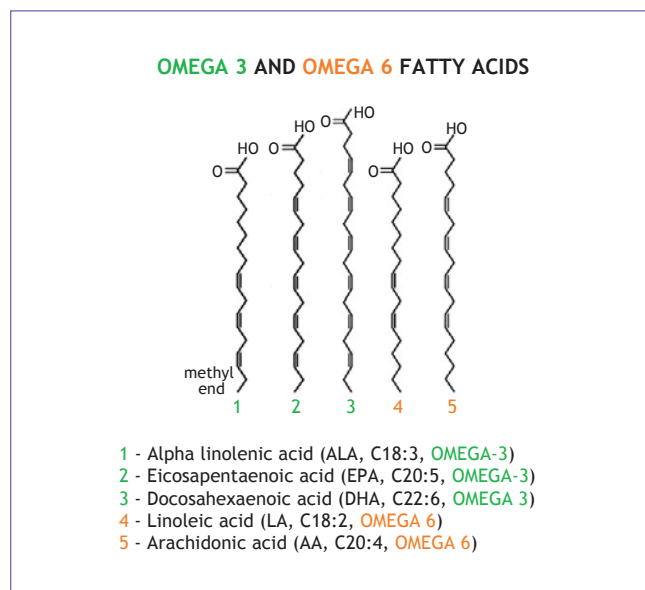


Figure 2. Main omega 3 and 6 fatty acids.

(EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3), both long-chain omega 3 FAs. However, this transformation is very limited and most EPA (90-95%) and DHA (almost 100%) are obtained from the diet<sup>4,5</sup>. Arachidonic acid (ARA, C20:4n-6), the main omega 6 FA, is also essential, although it is very abundant in animal fat (Fig. 2).

Docosahexaenoic acid is a main constituent of cell membrane phospholipids, especially in neural and retinal cells and spermatozooids, although it is also a producer of cell mediators, whereas EPA plays a more important role as a producer of cell mediators through its breakdown. The omega 3-rich foods are: fish (white but specially blue one), some dried fruits, shellfish (crustaceans and mollusks), green-leaf vegetables, some fruits such as avocado, flax, and pumpkin seeds, legumes and seed oils, especially soy, linseed, and canola oil (Fig. 3).

## POLYUNSATURATED FATTY ACID FUNCTIONS

Omega 3 and 6 PUFAs are essential for brain development in the fetal and postnatal periods<sup>6</sup> for neuronal growth, synaptic processing, and for the expression of genes that regulate cell differentiation and growth. In addition, they are essential for the development of the retina and the visual cortex<sup>7</sup>. Especially, omega 3 FAs are crucial for the synthesis of myelin and the maintenance of adult brain structure and functionality by providing more plasticity, permeability, and fluidity to cell membranes<sup>8</sup>. Fluidity is essential for better function of the cell membrane by allowing an adequate spatial coupling between receptors and their effectors. On the other hand, fluidity also determines excitability and nervous transmission capacity of the membrane. Fatty acids and cholesterol play a relevant role in the regulation of physicochemical properties of membranes. The higher the proportion of cholesterol and saturated FAs, the higher the rigidity will be, whereas higher proportions of DHA, ARA, and oleic acid allow for the membrane to be more fluid and permeable. On the other hand, by means of phospholipase, cyclo-

SOURCES OF OMEGA 3	
Fish	Salmon, Red mullet Herring, Bonito, Tuna, Cod, Sardine, Whitebait, Anchovy, Mackerel, Dogfish, Shark, Swordfish, Trout
Crustaceans and Mollusks	Crab, Shrimp, Clams, Lobster, Oysters, Mussels, Octopus, Squid, Cuttlefish, Sea Snails
Dried Fruits	Nuts Pistachio
Vegetables	Lettuce, Broccoli, Watercress, Collard, Greens, Spinach
Fruit	Avocado
Legumes	Grains, Beans, Peas, Soy, Oats
Oils	Soy, Linseed, Canola

Figure 3. Sources of omega 3.

oxygenase and lipoxygenase enzymatic action on EPA, mediators that participate in cell communication are generated. The substances resulting from enzymatic action on omega 3 and 6 PUFAs are prostaglandins, thromboxanes, and leukotrienes (eicosanoids) and new, recently discovered molecules (resolvins), whereas from EPA, eicosanoids of series 3 and 5 are obtained. From ARA, series 2 and 4 eicosanoids, with the last two showing a marked inflammatory nature. There is antagonism between omega 3 and omega 6 FAs with regard to their functions. Vasodilatation, inflammation, and coagulation, among other issues, will be affected according to their balance (Fig. 4).

This is why sufficient PUFA intake is as important as an adequate balance of omega 3 and 6 FAs since this will determine the synthesis of beneficial or noxious eicosanoids. A correct proportion between both will elicit anti-inflammatory, neuroprotective, and cardiovascular health preventive effects. The ideal dietary proportion between omega 6 and 3 FAs would be 3-4/1. If the intake of either one of them increases, the others will be proportionally reduced since both compounds compete with each other to turn into active metabolites in the body<sup>5</sup>.

In summary, PUFAs exert their multiple functions through three types of biological effects<sup>9</sup>:

- Effects caused by the bioactive mediators resulting from their breakdown through phospholipase A<sub>2</sub> initial effect and the subsequent participation of an entire enzymatic cascade that generates eicosanoids and resolvins, with the latter displaying high potency at minimal doses and acting as anti-inflammatory substances or in the resolution of inflammatory processes. This is of great interest to prevent all those inflammatory phenomena that are possible precursors of the cognitive deterioration that can be caused by the use of radio- or chemotherapy<sup>10,11</sup>.

- Direct effects resulting from cell membrane ion channels (calcium, sodium and potassium) interrelation<sup>12</sup> generate anti-arrhythmic effects that are different from those of traditional anti-arrhythmic agents.
- Effects by their direct incorporation to membrane phospholipids, which generates physicochemical changes that modulate receptors and proteins, or by direct action on nuclear receptors, with both situations resulting in an action on the genome and its expression<sup>13,14</sup>.

## OMEGA 3 AND NEUROCOGNITION

There is increasing evidence that suggests that an underlying pro-inflammatory and pro-oxidant state, favored by an

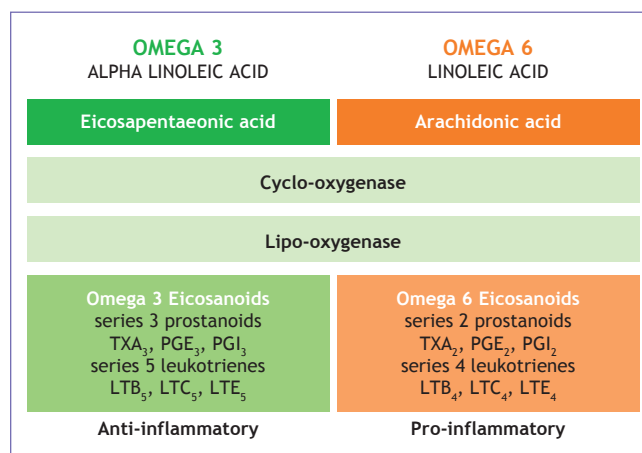


Figure 4. PUFA-derived antagonistic eicosanoids.

inadequate diet, is shared by age-related cognitive decline, Alzheimer's disease (AD), cardiovascular diseases (CVD), and cancer. Dietary lipid profile determines the composition and function of membranes, cell transmission, inflammatory processes, blood coagulability and atherogenicity, all being associated with cognitive function. The brain is one of the organs with the highest concentration of lipids (60%), especially DHA and ARA<sup>15</sup>. Although without entirely conclusive data, available evidence suggests that omega 3 FAs may play an important role in the prevention of brain damage. Evidence originating in biological and epidemiological studies indicates that reduced omega 3 PUFA intake is associated with a higher risk of dementia<sup>16-18</sup>. In animal models, dietary DHA increase delayed the expression of AD, improved cognitive performance, and decreased  $\beta$ -amyloid deposits<sup>19-21</sup>. Lower plasma and erythrocyte DHA concentrations have also been demonstrated in patients with AD<sup>22</sup>. These decreased DHA levels might be due to insufficient intake of this compound in particular, or also to reduced ingestion of mono-unsaturated FAs, such as oleic acid, which has been shown to be crucial for ingested DHA to fix to neuronal membrane phospholipids<sup>23</sup>. The most widely accepted theory about the cause of AD attributes the disease to abnormal deposits of  $\beta$ -amyloid and tau proteins in the brain of these patients, which produces a chronic inflammation that irreversibly damages the neurons. DHA has been shown to slow protein tau accumulation and to reduce  $\beta$ -amyloid levels, with this compound acting better alone than when administered together with omega 6 FA<sup>24</sup>. Currently, the most recent lines of investigation are focused on drugs that inhibit the production of prostaglandin E2 (PGE2) with the purpose of stopping AD chronic inflammation and  $\beta$ -amyloid accumulation<sup>25</sup>, but a more physiological alternative to stop this production could be dietary omega 3 PUFA intake.

## OMEGA 3 FATTY ACID NEUROPROTECTIVE MECHANISM

Several mechanisms have been proposed to explain omega 3 PUFAs protective function in cognitive deterioration. In the first place, they can protect by reducing the incidence of CVD and the risk for non-hemorrhagic stroke. In rebuttal of this hypothesis, a recent study that used PUFA supplements in patients with multiple cardiovascular risk factors failed to demonstrate any reduction in cardiovascular mortality and morbidity<sup>26</sup>. On the other hand, there is evidence that CVD increases the risk for dementia<sup>27-29</sup>. The benefits of long-chain PUFAs in the reduction of cardiovascular risk include the following effects<sup>9,27</sup>:

- Anti-arrhythmic effects; DHA alone or associated with EPA is a protective factor against arrhythmia and cardiac sudden death<sup>30,31</sup>;
- Anti-thrombotic effects<sup>32</sup>;
- Anti-inflammatory effects<sup>33,34</sup>;
- Anti-atherogenic effects<sup>35,26</sup>;
- Blood pressure-lowering effects<sup>37-39</sup>;
- Heart rate-lowering effects<sup>38,40</sup>;
- Endothelial function-enhancing effects<sup>41-43</sup>;
- They reduce the synthesis of pro-inflammatory cytokines, especially PGE2, interleukin 1 $\beta$  and tumor necrosis factor-alpha<sup>44-47</sup>;

- Other authors also indicate that PUFAs prevent glucose uptake difficulties in the aging brain, with this being a crucial factor in maintaining a good cognitive function<sup>48</sup>;
- Omega 3 FAs also reduce triglycerides (TG) hepatic synthesis, since they are poor substrates for the enzymes responsible of TG synthesis and they also inhibit other fatty acid esterification. Fatty acid  $\beta$ -oxidation increase in liver peroxisomes also contributes to TG decrease by reducing the amount of free fatty acids available for their synthesis. Inhibition of this synthesis decreases very low density lipoprotein<sup>30,49,50</sup>.

All these protective mechanisms might also prevent or avoid inflammatory phenomena caused by antineoplastic treatments<sup>51,52</sup>, and hence the interest in studying the role that omega 3 PUFAs might play in the prevention of cognitive damage in these patients.

Given that DHA is a primary component of the membrane phospholipids in the brain, adequate concentrations of omega 3 PUFA may protect against brain damage by protecting the membrane integrity and neuronal function. In animal models, dietary DHA increase has shown to facilitate neuronal membrane fluidity and excitability, to increase neurotransmitter levels, increase visual and auditory response, and reduce neuronal damage<sup>18</sup>. In behavioral models, this translated into a learning increase and higher memory performance in comparison with animals fed with control diet<sup>19,53</sup>. On the other hand, studies in animals and humans showed that an elevated caloric intake in the form of saturated FAs promotes the deposit of amyloid plaques<sup>54</sup>, whereas DHA-enriched diets decrease the accumulation of  $\beta$ -amyloid, its precursor protein, tau protein, and presenilin 1, thus protecting from dendrite loss<sup>24,54-56</sup>. On the other hand, EPA can counteract ARA's vasoconstrictor effects.

The absence of conclusive data on the optimal balance of DHA and EPA is noteworthy in neurocognitive impairment and CVD prevention<sup>27</sup>.

Omega 3 FAs also act on the functioning of neuronal systems that use dopamine and serotonin. By influencing these neurotransmitters, among other aspects, brain processes that control mood and anxiety can be affected<sup>57,58</sup>.

An exhaustive review of the Cochrane Collaboration about published studies on omega 3 FA neurocognitive preventive effect does not allow for a single conclusive study to be highlighted, since all have some methodological failure. But "the sum of several omega 3 PUFAs small protective effects can constitute a significant protective effect against age-related risk for dementia and cognitive decline"<sup>59</sup>. Based on available evidence from prospective epidemiologic cohort studies on the relationship between diet and lipid intake with cognitive deterioration and dementia, it can be concluded that high intake of PUFA, monosaturated FA, and omega 3 FA is a protective factor.

There are also randomized trials in elderly people with AD and some type of established dementia with PUFA dietary supplements<sup>60-63</sup>. In all of them, an improvement in neurocognitive functions, such as memory or learning capacity, is demonstrated (Table 1).

With regard to age-related cognitive decline prevention, there are three randomized trials with different PUFA doses and proportions, as well as with different intervention

**Table 1.** Published randomized trials with omega 3 supplements in cognitive deterioration

Study	Dose	Duration	Placebo	Tolerance	Sample
Yehuda, et al. <sup>60</sup>	Compound with 4/1 ratio between omega 6 and 3	1 month	Not described	Not described	100 pts. with AD
Terano, et al. <sup>61</sup>	0.720 g DHA	1 year	No	Not described	20 pts. with CV dementia
Freund-Levi, et al. <sup>62</sup>	1.7/0.6 g DHA/EPA	6 months	2.4 g LA (4 g corn oil)	Good	204 pts. with AD
Yurko-Mauro, et al. <sup>63</sup>	0.9 g DHA	24 weeks	50-50% corn and soy oil	Good	485 pts. with ARCD
Dangour, et al. <sup>64</sup>	0.5/0.2 g DHA/EPA	24 months	1.3 g olive oil	Good	867 pts. with ARCD
Van de Rest, et al. <sup>65</sup>	1.8 or 0.4 EPA/DHA	26 weeks	Sunflower oil	Good	302 pts. with ARCD

AD: Alzheimer's disease; ARCD: age-related cognitive decline; CV: cardiovascular; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; LA: linoleic acid; pts.: patients.

periods, which have failed to demonstrate their efficacy in this topic. Only one of the three trials has demonstrated improvement in memory and learning<sup>63-65</sup>. These unfavorable results can be attributed to different reasons such as sample size, doses and used proportions, degree of baseline cognitive impairment, intervention and follow-up periods, or even the placebo employed<sup>66</sup>.

There is an ongoing three-year interventional trial on cognitive impairment prevention, which plans to recruit 1,200 cognitively healthy elderly patients. There are four arms: one with multifactorial intervention, one with multifactorial intervention with omega 3 supplements, one only with omega 3, and the last one with placebo<sup>67</sup>.

An evidence-based report issued by the Agency for Healthcare Research and Quality suggested that "trials should be designed to assess omega 3 PUFA effects with the purpose to assess the effect of the omega 3 PUFA origin, dose, treatment duration, and effect maintenance after discontinuing their consumption". According to this report, "it is necessary to conduct adequately designed randomized controlled trials, with sufficient power and adequate duration (3-5-year supplementation and follow-up) with regard to dementia. These studies should include a baseline assessment on omega 3 and omega 6 PUFAs dietary consumption". Finally, the report also suggests that all studies should use standard validated instruments to assess clinical results<sup>68</sup>. Additionally, the type of fish consumed and the preparation method employed has to be taken into account in observational studies<sup>69</sup>.

Identifying randomized trials where cognitive deterioration prevention with omega 3 PUFA supplements is analyzed in cancer patients has not been possible, although, as previously showed, they might play a prominent protective role against radio- or chemotherapy related neurocognitive toxicity. With regard to the latter, the timing for initiation (before, during, or after therapy), the quantity, the proportion between PUFAs, and treatment duration might play a crucial role with regard to offering some benefit<sup>66</sup>.

Finally, it should be mentioned that interest is starting to exist in demonstrating the potential toxicity prevention and even survival improvement by using omega 3 supplements together with standard cancer therapies<sup>51,52</sup>.

## RECOMMENDATIONS ON OMEGA 3 DAILY INTAKE

There is great disparity between different institutions on the recommended dietary allowance (RDA). The UK Food Standards Agency current recommendations for non-reproductive age males and females are 1-4 servings of oily fish per week, in 140 g portions. The WHO recommends omega 3 PUFA 300-500 mg daily supplements<sup>9,70</sup>. The American Heart Association (AHA) recommends EPA and DHA 1 g/day mixed supplements in all those patients with coronary disease<sup>71,72</sup>, and approximately 500 mg/day for the rest, with these figures being consistent with the International Society for the Study of Fatty Acids and Lipids recommendation<sup>27</sup>. This dose is also associated with lower risk for coronary disease-associated death, as observed in multiple epidemiological studies in the USA<sup>27,72</sup>. The consumption of two servings of oily fish per week (approx. 300 g) would provide 4.9 g of omega 3 PUFA, which is equivalent to 700 mg/day. The Spanish Society of Community Nutrition (SENC - *Sociedad Española de Nutrición Comunitaria*) specifies that the DHA and EPA daily intake should be 200 mg. To cover the RDA, the SENC recommends the consumption of 3-4 servings of fish and shellfish per week (one serving = 125-150 g), 3-6 tablespoons of olive oil per day (30-60 ml), and 3-7 servings of dried fruits per week (one serving = 20-30 g). In France, a DHA daily intake of 120 and 100 mg is recommended for males and females, respectively. In the USA, the National Academy of Medicine recommends an EPA and DHA intake of 100 mg/day, whereas the Technical Committee on Dietary Lipids of the International Life Sciences Institute (ILSI) recommends an EPA + DHS RDA of 250-500 mg.

Let's observe which doses have demonstrated the beneficial effects of PUFAs in different situations:

- In severe inflammatory pathologies such as rheumatoid arthritis, high doses of 4-8 g/day are required<sup>73</sup>;
- Effective doses for attention deficit disorder with hyperactivity, anxiety, major depression<sup>74</sup>, bipolar disorder<sup>75</sup>, and postpartum depression seem to be around 1-2 g/day, while higher doses do not appear to be more efficacious<sup>58,76,77</sup>;
- Doses of 2-4 g are required in the prevention of CVD<sup>47,78</sup>;

- Doses of 0.5-2.0 g are necessary to obtain beneficial effects on arrhythmias<sup>27,79</sup>;
- TG anti-aggregation and reduction, especially in severe hypertriglyceridemia (> 500 mg/dl), require elevated doses of 3-4 g<sup>27,71,80</sup>.

With regard to intake recommendations, it should be noted that nutrient administration in the form of supplements does not necessarily have the same influence on the risk for dementia as the consumption of the same nutrients as part of the diet. The quality and proportions of nutrients naturally present in food have effects on absorption, metabolism, and ultimately on bioavailability, which are substantially different than would be expected with the administration of a single nutrient at pharmacological doses.

The intake of supplements will increase their concentrations, but there are non-dietary nutritional factors, such as absorption, metabolism, and genetic factors, that may affect human plasma and tissue concentration of FAs, without a proportional increase in the intake being produced<sup>81</sup>.

Finally, when assessing their bioavailability, the formulation of omega 3 supplements is crucial; there are the following presentations:

- Triglycerides (at concentrations of 70%, with this being the formulation with the highest bioavailability)<sup>5</sup>;
- In the form of ethyl or methyl esters (at concentrations between 50-70%)<sup>5</sup>;
- Or, in the form of free fatty acids<sup>9</sup>.

## TOLERANCE TO OMEGA 3 FATTY ACIDS

The USA ILSI Lipid Technical Committee concluded in 2008 that there is no evidence that the EPA plus DHA recommended intake is harmful. On the other hand, the FDA classifies the intake of omega 3 FAs originating from fish as safe in general terms, as demonstrated in several randomized clinical trials<sup>64,65</sup>.

The observed adverse effects are basically nausea, gastrointestinal discomfort, diarrhea, and fish-smelling breath; this is why their consumption is recommended during meals.

At dosages of 20 g/day, an increase in coagulation time has been observed in healthy volunteers, without associated hemorrhagic complications<sup>27</sup>. It has been concluded that doses higher than 7 g/day, mixing DHA plus EPA, are safe even with concomitant use of warfarin or anti-aggregants<sup>9,27,82</sup>. A prolongation of coagulation time is described associated with the use of 4 g, without significant bleeding episodes being produced. As a cautionary measure, periodic monitoring of all patients taking hemostasis-altering drugs is advised, with special attention to prothrombin time, which anyway is already routine practice.

Slight increases in blood sugar have also been observed in patients with type 2 diabetes mellitus, with no changes in HbA1c levels.

On the other hand, long-term consumption of fish oil in elevated quantities can cause vitamin E deficiency, and it is therefore added to many of these commercial preparations, but regular use of vitamin E-enriched products can also lead to elevated levels of this fat-soluble vitamin with the ensuing risk of overdosing<sup>9</sup>.

## CONFOUNDERS IN STUDIES ON COGNITIVE IMPAIRMENT PREVENTION

The ApoE gene is a pleomorphic gene with three main alleles: ApoE2, ApoE3 and ApoE4. It encodes for a protein that is essential for the catabolism of triglyceride-rich lipoproteins. This protein is the most important cholesterol transporter in the brain. ApoE proteins have been recognized for their importance in lipoprotein metabolism and in the development of CVD. The ApoE4 genotype has been associated with higher sensitivity to contract AD, to develop atherosclerosis, and to experience cognitive development deterioration. In addition, it is also associated with a lack of benefit after the consumption of PUFA-rich diets<sup>83</sup>, an observation that might explain the inconsistent results between studies and that reflects the importance of taking genetic factors into account in future studies<sup>66,84,85</sup>.

Finally, another potential confounder should be mentioned. Increased homocysteine plasma concentration is an important independent risk factor for atherosclerosis, coronary disease, death due to cardiovascular causes, stroke, dementia, and AD. Folic acid isolated administration or in combination with vitamins B<sub>12</sub> and B<sub>6</sub> can reduce its concentration<sup>86</sup>. Blood homocysteine should be determined in cognitive impairment prevention studies or all included patients should be supplemented with folic acid and vitamins B<sub>12</sub> and B<sub>6</sub>.

## CONCLUSION

Cancer incidence and prevalence are increasing, with an increase in long-term survivors thanks to therapeutic improvements. This results in an increased risk for neurotoxicity development. Any advance with regard to its prevention will be of utmost importance. Omega 3 PUFAs may play an important role in this line. These PUFAs are a major constituent of cell membrane, and especially of neural membrane, phospholipids. They are crucial for the synthesis of myelin and maintenance of the structure and functionality of the brain. In addition, they are producers of cell mediators involved in inflammatory processes. Their mechanisms of action are mainly based on the effects caused by bioactive mediators resulting from their breakdown, which act as anti-inflammatory substances, or on inflammatory process-resolution pathways. Another important aspect is their direct incorporation to membrane phospholipids. An adequate supplementation of omega 3 PUFAs might prevent cancer treatment-related neurotoxicity. No randomized trials on this subject could be found. When conducting this type of trial, the initiation timing (before, during, or after therapy), the amount, the proportion between omega 3 PUFAs, and treatment duration might play a crucial role. In addition, genetic and physico-chemical factors such as patient genotype with regard to the ApoE gene or homocysteine plasma concentration are highly important to avoid bias or confounding in the results. Interest is starting to exist in demonstrating possible toxicity prevention and even improved survival by using these types of supplements together with standard cancer therapies. In view of all that has been set forth above, well-designed studies on the use of omega 3 PUFA supplements will

be able to answer many of the posed questions with regard to anti-cancer therapy related neurocognitive damage.

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## DECLARATION OF INTEREST

There are no conflicts of interest relevant to the present work.

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