

Omega-3 fatty acids and cancers: a systematic update review of epidemiological studies

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Abstract

Experimental models showed consistently a modulation of carcinogenesis by omega 3 polyunsaturated fatty acids (ω 3 PUFA). Fish intake is often described as part of a beneficial dietary pattern. However, observational epidemiological studies on the relationship between ω 3 PUFA reported conflicting results. The objective of this systematic review is to determine whether there exists any progress in the evaluation of the causal relationship between dietary ω 3 PUFA and cancers since the previous FAO/OMS expert consultation and whether it is possible to propose preventive and/or adjuvant therapeutic recommendations. Prospective and case-control observational studies published since 2007 and meeting validity criteria were considered together with RCT. Experimental studies are mentioned to provide for biological plausibility. When evaluating the level of evidence, a portfolio approach was used, weighted by a hierarchy giving higher importance to prospective studies followed by RCT if any. There is a probable level of evidence that ALA *per se* is neither a risk factor nor a beneficial factor with regards to cancers. Observational studies on colorectal, prostate and breast cancers only provided limited evidence suggesting a possible role of LC- ω 3PUFA in cancer prevention because insufficient homogeneity of the observations. Explanation for heterogeneity might be the inherent difficulties associated with epidemiology (confounding and dietary pattern context, measurement error, level of intake, genetic polymorphism). The role of LC- ω 3PUFA as adjuvant, might be considered of possible use, in view of the latest RCT on lung cancers even if RCT on other cancers still need to be undertaken.

Key words: Omega 3 fatty acids: EPA: DHA: alpha linolenic acid: cancers: epidemiologic studies

Rationale: The incidence of cancers affected almost 13 million people and caused more than 7 million deaths worldwide in 2008. Incidence is expected to increase to 15 million in 2015 and death to more than 9 million due to demographic effects alone. However increased longevity is not the only explanation, e.g. in France the incidence of cancers in males increased by 35% and in females by 43% after controlling for the demographic effect⁽¹⁾ Thus it is generally acknowledged that changes in exposure to carcinogenic environment and in nutrition are factors of this evolution.

If changes in food patterns are more often associated with an increased incidence of cancers, as illustrated in migrant studies⁽²⁾, it happens that nutritional recommendations are followed by a decreased incidence⁽³⁾. This underlines the search for beneficial nutrients. Several epidemiological studies have shown a risk reduction of some cancers associated with long chain omega3 fatty acids (ω 3 LC-PUFA) or fish intake⁽⁴⁾, but the limited evidence or the absence of consistency required further investigations.

A systematic review of the epidemiological studies published since 2007 is undertaken here focusing on ω 3 LC-PUFA either from dietary intake (but not considering fish) or from plasma or cellular markers. As in the FAO/WHO

joint expert consultation⁽⁴⁾, the most common cancers, colorectal, prostate and breast cancers are covered, and a paragraph on other cancers has been added. Use of ω 3 LC-PUFA as adjuvant therapy of cancers will also be considered.

Objectives

This update review focused on studies published not taken into account in the previous FAO/OMS expert consultation⁽⁴⁾ to determine whether there exists any progress in the evaluation of the causal relationship between dietary ω 3 PUFA and cancers and whether it is possible to propose preventive and/or adjuvant therapeutic recommendations.

Methods

Types of studies and eligibility criteria

In the complex field of cancer and nutrition, taking into consideration all studies available (mosaic or portfolio approach⁽⁵⁾) is necessary. All prospective and case-control observational studies published since the ones reported in the FAO/WHO joint expert consultation⁽⁴⁾ were considered. Intervention studies and randomised controlled trials (RCT)

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when they exist were also considered. *In vivo* or *in vitro* experimental studies are mentioned to provide for biological plausibility. All these studies must meet validity criteria, such as population and sample size, ascertainment of disease diagnosis, quality of exposure measurement, (questionnaire characteristics – interview, self-administered, number of items, food groups-, or relevancy of biological markers), quality of statistics (adjustment for confounding factors). Population and sample size, quality of exposure measurement, quality of statistics (adjustment for confounding factors) and specific remarks are shown in corresponding tables. Excluded invalid studies were referenced and their exclusion is justified.

When evaluating the level of evidence, a hierarchy among studies has been proposed to help to establish a causal inference⁽⁶⁾. Top of the hierarchy is data from prospective studies, which then might be supported by intervention studies, when they exist. Case-control studies are judged by these authors to be in third position, followed by experimental studies. However, each study of the portfolio have to be weighted, and in this perspective, it is acknowledged that prospective studies have the highest weighting.

Finally, the World Cancer Research Fund/American Institute for Cancer Research in 2007 proposed criteria for grading evidence⁽⁷⁾:

- *Convincing* (unlikely to be modified by further studies): evidence from more than one type of study and from at least two prospective cohort studies; no substantial unexplained heterogeneity within or between studies types or in different populations; valid studies (as defined above); dose response effect, not necessarily linear as long as the explanation is biologically plausible; strong experimental evidence (human or animal) that exposure to the factor can lead to the disease.
- *Probable*: the same as the points above except for the first one: evidence from at least two prospective cohort studies or at least five case-control studies;
- *Limited-suggestive*: not enough studies, or studies with methodological flaws, but show generally consistent direction of effect, in spite of some unexplained heterogeneity.
- *Limited-no conclusion* evidence so limited that no firm conclusion can be made.
- *Substantial effect on risk unlikely*: the same as convincing but with studies showing absence of effect.

When the level of evidence is judged convincing or probable, preventive recommendations should be made in the perspective of public health.

Information sources

MEDLINE, via PubMed®, was searched between 1–15 April, 2011 back to 2007 in order to update the FAO/OMS expertise⁽⁴⁾ with the following strategy for each considered cancer: omega 3 fatty acids, fish intake, fish oil. For the database LILACS, the same word with the all words strategy was used. The studies reporting on fish were only included if the relationship with cancer incidence was specifically expressed as omega3 fatty acids. Whenever possible, distinction is

made between α -linolenic acid (18:3 n-3, ALA) and LC ω 3 PUFA, and among them eicosapentaenoic acid (20:5 n-3, EPA) and docosahexaenoic acid (22:6 n-3, DHA)

Colorectal cancer

Food and nutrition play an important role in colorectal cancer development among the factors related to high income, industrialization and urbanization, hence prevention may be implemented. The studies covered in the expert consultation of FAO on fatty acids⁽⁴⁾ suggest a probable causal relationship between fish intake and CRC. However, evidence was too limited to draw any firm conclusion on the effect of LC ω 3 PUFA.

Four case-control studies have been published: Kato et al⁽⁸⁾ was excluded for insufficient characterisation of the omega 3 intake, the others^(9–11) are presented in Table 1, Table 2 describes the results of the recent prospective studies^(12–17)

ALA

Two case-control studies^(10,11) out of 2, (Table 1) showed no effect, as did one European⁽¹²⁾, and one Japanese⁽¹⁵⁾ prospective cohorts, whereas another American one⁽¹⁶⁾ showed a significant increase in risk (Table 2). However, when further adjustment was made for meat, the RR decreases, and the trend was no longer significant, alluding to the confounding effect of meat rich in ALA, because of the soya feed given to livestock. Thus, there is no firm conclusion, but a limited evidence for an absence of relationship.

LC ω 3 PUFA

The 3 case-control studies^(9–11) showed a decreased risk associated with the highest quantile of LC- ω 3PUFA intake, in spite of strong difference in intake between the 3 studies (Table 1). Results of the 6 prospective studies are conflicting with 1 study⁽¹⁶⁾ reporting no effect, one⁽¹⁷⁾ an increased risk, and 3^(13–15) reporting a reduced risk. One of these 3 studies⁽¹³⁾, a subgroup of the Physician Health Study⁽¹⁴⁾ based on biological markers, reported a reduced risk, only in subjects not taking aspirin. The Japanese study⁽¹⁵⁾ reporting a reduced risk, analysed a large number of sub-groups, giving rise to different results between men and women, stage and sites of the disease, which might lead spurious findings, in spite of the quality of the study. A subsequent study⁽¹⁸⁾ of the Chinese population of Singapore⁽¹⁷⁾, showing an increased risk associated with a high intake of LC ω 3 PUFA, reported that the positive association between high intake of marine n-3 PUFA and rectal cancer risk was observed among carriers of at least one *PARP* codon 762 Ala allele (OR: 1.7, CI: 1.1–2.7) without indicating whether this SNP is frequent in Singapore Chinese. The role of eventual chemical contaminants might be also evoked to explain this increased risk⁽¹⁹⁾

Compared to the complex colorectal cancer picture, with various subsites and stages, and avoiding the measurement error of questionnaire, an endoscopy-based case-control study on colorectal adenomas with serum level measurement of fatty acids represents a simpler situation to apprehend⁽²⁰⁾.

Table 1. Omega 3 fatty acids and colorectal cancer risk (incidence): case-control studies

Author, year country	Subjects and methods	Exposure measurement	ALA*	Omega 3 LC-PUFA* (g/day)	Remarks
Kimura <i>et al.</i> ⁽⁹⁾ , 2007, Japan	782 CRC 793 population-based controls	FFQ by interview, 148 items		H (3.94) vs L (1.99) 0.74 (0.52–1.06) T: 0.05 distal CC: 0.56 (0.34–0.92) T: 0.02	ω 3/ ω 6:H (\geq 0.28) vs L (<0.17) 0.63 (0.49–0.80) T < 0.0005
Theodoratou <i>et al.</i> ⁽¹⁰⁾ , 2007, UK, Scotland	1455 CRC 1455 population-based controls M/F	Self-administered FFQ, 150 items	H (\geq 1.545) vs L (<1.128) 0.97(0.76–1.24)	EPA: H (\geq 0.442) vs L (0–0.167) 0.62 (0.49–0.79) T: < 0.0005 DHA H (\geq 0.587) vs L (<0.234): 0.63 (0.51–0.83) T: <0.0005	ω 6/LC- ω 3:H (\geq 254.7) vs L (<90.3) 1.42 (1.04–1.95) T < 0.02
Kim <i>et al.</i> ⁽¹¹⁾ , 2010, USA	White: 716 CC 787 Black:213 CC/156 population-based controls	NIH diet history Questionnaire by interview, 124 items	H (\geq 2.13) vs L (<1.16) 1.03 (0.66–1.60)	H (\geq 0.18) vs L (<0.06) 0.61 (0.44–0.86) T < 0.01 EPA:H (\geq 0.05) vs L (0 < 0.01) 0.65 (0.47–0.91) T: < 0.01 DHA H (\geq 0.11) vs L (<0.04): 0.58 (0.41–0.81) T: <0.01	

OR (CI): estimated relative risk (confidence interval); ALA, alpha-linolenic acid; omega 3 LC-PUFA, omega3 long chain-polyunsaturated fatty acids; CC, colon cancer; RC, rectum cancer; M, males; F, females; FFQ, food frequency questionnaire; CRC, colorectal cancer; H, highest quantile; L, lowest quantile; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; T, trend; NIH, National Institute of Health.

In such a study, total serum n-3PUFA levels were inversely associated with colorectal adenoma risk, the OR comparing the third tertile with the first tertile was 0.67 (0.46–0.96), trend: 0.03.

Given that results are rather consistent when fish intake is considered⁽⁴⁾, one could expect comparable observations, serum LC- ω 3PUFA being highly correlated with fish intake^(14,21). Several experimental studies support the hypothesis of CRC risk reduction by LC ω 3 PUFA^(22–25) through different mechanisms. In addition, the hypothesis of the anti-inflammatory effect of LC- ω 3PUFA and especially EPA⁽²⁶⁾ is supported by the subgroup study nested in the PHS, based on biomarkers⁽¹³⁾, showing a significant interaction with the absence of aspirin treatment (Table 2). However, epidemiological studies are as yet inconsistent, revealing the difficulty of studies focusing on one specific type of nutrient within the context of a multifactorial disease and subjected to confounding and imprecision of exposure measurement.

Thus, it can be said that limited evidence, supported mainly by case-control studies, experimental studies and biological plausibility, suggests a possible relationship between LC- ω 3PUFA and CRC.

Prostate cancer

Prostate cancer (PC) is the 2nd most common cancer in men, accounting for around 12% of all new cases of cancers in the world. Screening for prostate specific antigen (PSA) is in part responsible for its high incidence in high-income countries. As for CRC, the expert consultation of FAO on fatty acids (4) recognised heterogeneity in the considered studies and could not conclude on the existence of a relationship.

Prostate cancer is generally recognized as a hormone-dependent cancer, and to vary with ethnic characteristics, a higher incidence being observed in Afro-American men. However, comparative studies of African Americans in Washington, D.C. and Nigerians in Ibadan demonstrated similar incidence of latent prostate cancer, although the African Americans recorded a 10-fold higher incidence of clinical prostate cancer. Differences observed between healthy indigenous Africans and African Americans in their levels of estrogen and androgen metabolites and urinary steroids were reported to depend on their respective diets and could explain their disparate PC rates as suggested by a comparative study conducted in these populations (48 cases, 96 population based controls Afro-Americans; 66 cases, 266 population based controls Nigerians)⁽²⁷⁾. This study was designed as a case-control study based on fatty acids biomarkers showed that total omega 3 fatty acids were significantly higher in Nigerian than in Afro-Americans ($p < 0.01$). However estimation of the relative risk suffered from the low power of the study because of the small sample (12 to 15 cases by quartile) and could not be retained in the evaluation of the association of PC with omega 3 fatty acids. Another case-control study⁽²⁸⁾ with a small sample (79 cases, 12 to 19 cases by tertiles of the subgroups) cannot be interpreted, with findings bearing only on the ratio ω 6/ ω 3. Retained studies are displayed on Tables 3 and 4.

Table 2. Omega 3 fatty acids and colorectal cancer risk (incidence): prospective studies

Author, year, country	Subjects and methods	Exposure measurement	ALA*	ω 3 LC-PUFA*	Remarks
Weijenberg <i>et al.</i> , 2007, Netherlands ⁽¹²⁾	401 CC; 130 CR/120852 Follow-up: 7.3 years	Validated FFQ, 150 items Database TRANSFAIR	g/day: H (M: 2.0 F 1.6): vs L (0.8; 0.6) CC 1.01 (0.76–1.36) CR 0.92 (0.58–1.44)		
Hall <i>et al.</i> , 2007, USA ⁽¹³⁾	Men 178 CCR/282 481 controls nested in the Physician Health Study Follow-up up to 13 years	Total blood FA			M without aspirin: ω -3 LC PUFA: 0.34 (0.15–0.82) T: 0.006 interaction 0.04 M with aspirin 1.09 (0.48–2.50). RR # for CC and RC Limits of quartiles not given
Hall <i>et al.</i> , 2008 USA ⁽¹⁴⁾	500 CRC/21,406 the Physician Health Study Follow-up 22 y	Short FFQ + sea-food consumption Validation Adipose issue EPA + DHA		0.76 (0.59–0.98) T: 0.02	
Sasazuki <i>et al.</i> , 2009 Japan ⁽¹⁵⁾	1268 CCR/98,466 (M: 521 CC, 253 RC; F: 350 CC, 144 RC) Follow-up 9.3 years	Validated FFQ, 138 items EPA, DPA and DHA sum marized as marine n-3 PUFAs	g/day M: H (med 2.76) vs L (1.21) 0.84 (0.56–1.28) T NS F H (med 2.64) vs L (1.35) 1.01 (0.65–1.57) T NS		M invasive, proximal CC: EPA: 0.27 (0.11–0.66) T: 0.01 DHA: NS W: NS
Daniel <i>et al.</i> , 2009, USA ⁽¹⁶⁾	Follow-up 6 years 869 CCR (452 M, 417 F)/99,080 (43,108 M, 55,972 F).	Validated FFQ, 152 items	g/day H (≥ 1.19) vs L (<0.78) 1.46 (1.09–1.95) T: 0.04		In the multivariate model controlling for meat ALA 1.38 (1.02–1.85) T: NS ω 3/ ω 6:H (med. Q 0.07) vs L (0.02) 1.45 (1.12, 1.87) T: 0.01
Butler <i>et al.</i> , 2009, Singapore ⁽¹⁷⁾	Follow-up 9.8 years CCR 961/61321 Chinese	Validated FFQ, 165 items, 14 sea-food items		Advanced cancer H (med. Q: 0.29 g/1000 kcal) vs L (0.09) 1.33 (1.05–1.70) T: <0.01	

* RR (CI): relative risk (confidence interval); ALA, alpha-linolenic acid; omega 3 LC-PUFA, omega 3 long chain-polyunsaturated fatty acids; CC, colon cancer; RC, rectum cancer; M, males; F, females; FFQ, food frequency questionnaire; CRC, colorectal cancer; H, highest quantile; L, lowest quantile; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; TFA, total fatty acids; T, trend; NS, non significant.

ALA

Two case-control studies^(29,30) in Table 3 and 4 prospective ones in Table 4^(31–34) reported conflicting results: the 2 case-control studies^(29,30) and one⁽³³⁾ among the 4 prospective cohorts showed no association of PC with ALA. One prospective study⁽³²⁾ showed a reduced risk and 2^(29,34) an increased PC risk related to ALA intake. A pooled analysis⁽³⁵⁾ concluded that the absence of relationship between ALA and PC was very likely, with a limited probability of a weak positive effect. There are neither biological plausibility nor experimental models supporting a deleterious effect of ALA. Therefore, it is likely that the risk associated to high intake in some studies results from residual confounding. Cattle being fed with soy, rich in ALA, could be responsible for the residual confounding, this fatty acid could be confounded by the limited but suggestive risk associated with processed meat, milk and dairy products.

LC ω 3 PUFA

One⁽³⁰⁾ of the 2 case-control studies^(29,30) and one⁽³²⁾ of the 3 prospective studies^(32–34) showed no association with the sum of LC- ω 3PUFA, the other case-control study⁽²⁹⁾ and one prospective study⁽³⁴⁾, showed a risk reduction of PC for the highest quantile of LC- ω 3PUFA and of each of LC- ω 3PUFA intake. The results of the case-control study⁽²⁹⁾ showed an interaction between the LC- ω 3PUFA and each LC- ω 3PUFA, and a variant of the COX-2, modifying the effect of the intake. The results of the prospective study are of interest because the exposure measurement is assessed by biomarkers, avoiding measurement error, and results are consistent in spite of the many analyses conducted. One prospective⁽³³⁾ study showed an increased risk for a very high intake (median of the quartile 1.3 g/day) of LC ω 3 PUFA. This result might be considered in the light of possible fish environmental contaminants⁽¹⁹⁾.

The biological plausibility from experimental studies^(25,36), especially involving the anti-inflammatory effects of PUFAs, possibly through mediation of cyclooxygenase (COX), a key enzyme in fatty acid metabolism and inflammation⁽²⁶⁾, is supported by the case-control study⁽²⁹⁾ showing that the subjects carrying a mutation of the gene COX 2 needed a higher intake of EPA + DHA to be protected than the subjects carrying the most common gene.

Thus, epidemiological studies provide inconsistent results suggesting an inverse association of LC ω 3 PUFA. However, the heterogeneity could be explained by measurement errors, insufficient food composition tables, high intake of fish possibly contaminated by endocrine disruptors, statistical difficulty at disentangling specific fatty acids, which are correlated in the intake and expressed as % when measured in blood.

Breast cancer

Breast cancer (BC) is the most common cancer in women worldwide. Hormone metabolism is the preponderant influential factor for BC: high estradiol, either from endogenous

Table 3. Omega 3 fatty acids and prostate cancer risk (incidence): case-control studies

Author, year, country	Subjects and methods	Exposure measurement	ALA*	ω 3 LC-PUFA*	Remarks
Fradet <i>et al.</i> ⁽²⁹⁾ , 2009, USA	466 cases, 478 matched hospital based controls	Validated FFOQ	H (2.55 g/d vs L (0.79) 0.81 (0.48–1.35) T: 0.11	H (0.588 g/d/ vs L (0.067) 0.37 (0.25–54) T: 0 <0.0001 EPA H (0.167 g/d/ vs L (0.020) 0.35 (0.24–0.52) T <0.0001 DPA H (0.061 g/d/ vs L 0.008) 0.39 (0.18–0.85) T <0.0001 DHA H (0.368 g/d/ vs L 0.037) 0.36 (0.25–0.53) T <0.0001	Subjects with rs4648310 (+8897 A > G) SNP in COX-2: inter-action: <i>p</i> = 0.02 stratification on consumption of ω 3 LC-PUFA H (0.588 g/d) 0.61 (0.46–0.81) L: (0.067 g/d) 5.49 (1.80–16.7)
Shannon <i>et al.</i> ⁽³⁰⁾ , 2010, USA	127 cases, 185 hospital-based screen PSA negative controls	Erythrocytes fatty acids	H, (>0, 135% TFA) vs L (<0.107) 0.72(0.41–1.28)	EPA H (>0.47% TFA) vs L (0.35) 1.12 (0.64–1.96) T: NS DHA: H (>3.67%) vs L (<2.99) 1.06 (0.48–2.32) T: NS	

OR (CI): estimated relative risk (confidence interval); ALA, alpha-linolenic acid; omega 3 LC-PUFA, omega 3 long chain-polyunsaturated fatty acids; FFOQ, food frequency questionnaire; H, highest quantile; L, lowest quantile; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; T, trend; DHA, docosahexaenoic acid; PSA, prostate specific antigen; TFA, total fatty acids; NS, non significant.

(high synthesis and/or altered regulation of binding proteins) or exogenous sources is the major risk factor. Most of the lifestyle factors modify BC risk through their effect on hormone metabolism as well as others factors related to industrialization and urbanization. These factors encompass societal changes such as women's sexual liberation and entrance in the working world, resulting in late age at births, low parity and low frequency of lactation; they encompass also, possible environmental factors such as endocrine disruptors. Altogether, these lifestyle, societal, and possible environmental factors participate in the high incidence of BC in high-income countries, and in the rapidly increasing incidence in emergent and low-income countries. Nutrition is only one amongst these numerous factors, but also one that is the easiest to modify. So far, except for energy imbalance and development of obesity, there is not strong evidence for nutritional recommendation with regard to BC. Four case-control studies are reported in Table 5 and 6 prospective studies in Table 6.

ALA

There is no association between ALA and BC in Asian countries^(37,41,44) It is found in the French study⁽⁴⁰⁾ that BC risk is reduced when the source of ALA is vegetable oil, but increased when the source of ALA is processed food (Table 6). This suggests, as in other cancers, that the relationship of ALA with cancers is likely to be confounded by some components in foods. These foods could be part of a Western dietary pattern and not of Asian dietary pattern. Hence, ALA *per se* is probably not associated with breast cancer.

LC ω 3 PUFA

Results are rather consistent both from case controls and from prospective cohorts studies from Asian countries showing a risk reduction associated with intake of LC ω 3 PUFA^(37–39,41) with one exception⁽⁴⁴⁾. There is also a risk reduction in a study conducted in USA for the fish oil current users⁽⁴³⁾. There is no association observed in European countries^(40,42) (Tables 5 and 6). The heterogeneity could be explained by a difference in exposure. The median intake reported in the negative Chinese study⁽⁴⁴⁾ is 200 mg/day whereas it is from 300 mg up to more than 500 mg in other Asian studies. The North-American⁽⁴³⁾ study showing an association is based on the effect of supplementation with fish oil. Considered together, these studies indicate the possible necessity of a high intake of LC- ω 3PUFA to show an association.

These observations might be reinforced by 2 studies on BC and fibrocystic disease^(39,45) and one on BC prognosis⁽⁴⁶⁾ The first one was a case-control study that determined erythrocyte fatty acid concentrations in 155 women with non proliferative fibrocystic disease (NPFC), 185 women with proliferative fibrocystic disease (PFC), 241 women with BC, and 1,030 control subjects. The results related to BC are reported in Table 5⁽³⁹⁾ and showed that EPA reduced the risk of progressing from PFC to BC. The study showed also that EPA reduced the risk of NPFC (0.33 CI: 0.18–0.61, T: 0.0001). In a more recent study⁽⁴⁵⁾, the same authors observed an inverse

Table 4. Omega 3 fatty acids and prostate cancer risk (incidence): cohort studies

Author, year country	Subjects and methods	Exposure measurement	ALA*	ω 3 LC-PUFA*	EPA	DPA	DHA
Giovanucci <i>et al.</i> ⁽³¹⁾ , 2007, USA	Follow-up 15 years 3544 caes/47750 localized: 2161 advanced 523 fatal: 312	Validated self-administered FFQ 131 items	H (≥ 1.32 g/d) vs L (0.70) 1.12 (0.98–1.29) 1.57 (1.19–2.07) 1.53 (1.07–2.20)				
Park <i>et al.</i> ⁽³²⁾ , 2007 USA	Multiethnic 4404/82483 advanced 1278 Follow-up 8 years	Validated, self-administered FFQ 180 items	H median (1.07 g /1000 kcal) vs L (0.55) 0.92 (0.84–1.02) 0.89 (0.74–1.06) all Caucasians cases: 0.70 (0.64–0.99) T = 0.06 Hispanics: 0.83 (0.67–1.01) T = 0.03	H median (0.107 g/1000 kc) vs L (0.014) 1.01 (0.91–1.13) 1.05 (0.86–1.28)			
Wallström <i>et al.</i> ⁽³³⁾ , 2007, Sweden	Follow-up 11 years 817 /10564 advanced: 281	Interview-based, combined 7-day menu-book and FFQ 168-items	H med. (1.4 g/d) vs L (2.7) 0.92 (0.73–1.15) 0.93 (0.64–1.36)		H med (0.44/d) vs L (0.03) 1.28 (1.02–1.61) T:0.07 0.95 (0.65–1.40) T NS		H (0.86 g/d) vs L (0.12) 1.29 (1.02–1.64) T:0.05 0.91 (0.61–1.37) T NS
Chavarro <i>et al.</i> ⁽³⁴⁾ , 2007 USA	Follow-up 13 years 476 case/476 matched controls nested in PHS cohort 289 localised cases 244 cases Gleason < 7 209 non aggressive tumors 108 advanced cases 130 cases Gleason ≥ 7 221 aggressive tumors	blood	H (0.54 % TFA) vs L (0.24) 1.31 (0.89–1.95) T NS 1.66 (1.02–2.71) T :0.05 1.56 (0.90–2.71) T NS 1.73 (0.98–3.07) T 0.09 1.04 (0.45–2.38) T NS 1.49 (0.67–3.27) T NS 1.14 (0.64–2.03) T NS	H (6.70 % TFA) vs L (3.66) 0.62 (0.41–0.95) T:0.03 0.52 (0.28–0.94) T:0.04 0.58 (0.31–1.10) T :0.08 0.61 (0.31–1.20) T : 0.10 1.03 (0.41–2.63) T NS 0.63 (0.26–1.55) T NS 0.56 (0.27–1.13) T:0.03	H (2.36 %TFA) vs L (1.28) 0.57 (0.36–0.92) T:0.02 0.46 (0.24–0.86) T0.02 0.57 (0.28–1.11) T:0.07 0.58 (0.28–1.17) T NS 1.27 (0.49–3.29) T NS 0.42 (0.1–.14) T:0.07 0.61 (0.30–1.25) T : 0.09	H (1.19 %TFA) vs L (0.77) 0.60 (0.38–0.93) T :0.01 0.46 (0.26–0.83) T :0.003 0.72(0.39–1.32) T :NS 0.62 (0.32–1.21) T :NS 0.72 (0.30–1.73) T :NS 0.30 (0.12–0.80) T : 0.008 0.42 (0.21–0.83) T :0.004	H (3.37 %TFA) vs L (1.42) 0.60 (0.39–0.93) T :0.07 0.53 (0.30–0.94) T : 0.02 0.64 (0.35–1.17)T :NS 0.64 (0.33–1.24) T :NS 0.98 (0.39–2.50) T :NS 0.53 (0.21–1.31) T :NS 0.53 (0.26–1.05) T : 0.16

*RR (CI): relative risk (confidence interval); ALA, alpha-linolenic acid; omega 3 LC-PUFA, omega3 long chain-polyunsaturated fatty acids; FFQ, food frequency questionnaire; CRC, colorectal cancer; H, highest quantile L, lowest quantile; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PHS, Physician Health Study; TFA, total fatty acids; T: trend; NS, non significant.

Table 5. Omega 3 fatty acids and breast cancer risk (incidence): case-control studies

Author, year, country	Subjects and methods	Exposure assess.	ALA*	ω 3 LC-PUFA	EPA*	DHA	Remarks
Kuriki <i>et al.</i> , 2007 ⁽⁹⁷⁾ , Japan	Cases 103 controls/309	Validated FFQ 47 items		H (> 0.55 g/1000 kcal) vs L (< 0.36) 0.51; (0.27–0.98) T: < 0.05			<i>n</i> -6 PUFAs/ <i>n</i> -3 PUFAs, H (> 18.50) vs L (< 12.46)) 1.66 (0.89–3.09)
Kuriki <i>et al.</i> , 2007 ⁽⁹⁷⁾ , Japan	103 cases/309 controls (all from out-patient clinic)	Erythrocyte-membranes	H (> 0.39% TFA) vs L (< 0.26) 0.69 (0.37–1.28)	H (> 1.39% TFA) vs L (< 0.89) 0.27 (0.14–0.53) T < 0.0001	H (> 4.79 TFA % vs L (< 3.46) 0.06 (0.02–0.16) T < 0.0001	<i>n</i> -6 PUFAs/ <i>n</i> -3 PUFAs, H (> 3.65 vs L > 2.82) 5.74 (2.69–12.27) T: < 0.0001	
Kim <i>et al.</i> , 2009 ⁽⁹⁸⁾ , South Korea	Cases 358/hospital-based controls 360 Pre-Mp (210/196)	Validated FFQ interview 103 items		H (\geq 101 mg/d) vs L (< 10) 0.50 (0.28–0.91) T: 0.016	H \geq 213 mg/d) vs L (< 37) 0.44 (0.24–0.79) T: 0.004		
Shannon <i>et al.</i> , 2009 ⁽⁹⁹⁾ , China	241 women with breast cancer/185 PFC	Erythrocytes membranes		0.67 (0.30–1.50) T: NS H (0.69 TFA %) vs L (0.46) 0.38 (0.30–1.50) T: 0.035 0.51 (0.27, 0.94) T: 0.003	0.54 (0.24–0.79) T: 0.118 0.32 (0.24–0.79) T: 0.010 H (> 5.46 TFA %) vs L (\leq 4.40) 0.58 (0.33, 1.01) T: 0.06	ALA + ω 3 LC-PUFA: H (> 8.36%) vs L (\leq 7.05) 0.57 (0.32, 1.00) T: 0.04	

RR (CI): relative risk (confidence interval); ALA, alpha-linolenic acid; omega 3 LC-PUFA, omega3 long chain-polysaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FFQ, food frequency questionnaire; H, highest quantile; L, lowest quantile; Mnp, menopausal; PFC, Proliferative cystic disease.

association between fibroadenoma and higher percentages of the RBC EPA and DHA (0.38 CI 0.19–0.77, T: 0.007 and 0.32 CI 0.15–0.70 T: 0.024, respectively) in a case (248)-control (1035) study on fibroadenoma risk. Association between dietary intake of EPA and DHA from food and supplements, and disease-free survival and overall survival was examined⁽⁴⁶⁾ Women with higher intakes of EPA and DHA from food had an approximate 25% reduced risk of additional breast cancer events: (tertile 3: HR: 0.72, 0.57–0.90) compared with the lowest tertile of intake. Women with higher intakes of EPA and DHA from food had a dose-dependent reduced risk of all-cause mortality: tertile 3: HR = 0.59 (95% CI = 0.43–0.82). EPA and DHA intake from fish oil supplements was not associated with breast cancer outcomes. Thus, EPA and DHA but also another nutrient in fish, appeared to be associated with reduced risk of additional breast cancer events and all-cause mortality. Experimental studies^(24,47) support the biological plausibility of this association. Some of the experimental studies tend to allot the most important role to DHA, through regulation of gene transcription^(25,48).

Thus, there is increasing evidence suggesting an association between BC and LC ω 3 PUFA, with a possible explanation of the heterogeneity by the amount of the intake and the dietary pattern context. These more recent results seem to confirm an earlier meta-analysis⁽⁴⁹⁾ showing an association between LC- ω 3PUFA and BC (RR: 0.61, CI 0.40–0.93) for all women in the considered cohorts, and more especially for post menopausal women (RR: 0.58, CI 0.52–0.64).

Other cancers

There are far fewer studies on other cancers and omega 3 fat acids. One study⁽⁵⁰⁾ compared the level of ALA and LC- ω 3PUFA in plasma phospholipids and cholesteryl esters in 71 newly diagnosed, untreated cancer patients of three tumour types: oesophageal or cardia cancer (*n* 35), non-small cell lung cancer (*n* 22) and pancreatic cancer (*n* 15) and in 45 healthy subjects. Only patients with *pancreatic cancer* presented significantly lower levels of EPA and DPA compared to healthy subjects and to other cancers. In a systematic review⁽⁵¹⁾, it was concluded that there were no significant associations between omega-3 fatty acid consumption and cancer incidence for upper respiratory-digestive cancers, bladder cancer, lymphoma, ovarian cancer, pancreatic cancer, or stomach cancer. Not enough studies have been undertaken to modify this conclusion.

A study⁽⁵¹⁾ (532 cases and 1701 population-based controls) was conducted in the USA and showed an increased risk for *pancreatic cancer* (OR: 1.5, CI: 1.1–2.0, T: 0.02) for an ALA intake \geq 1.4 g/day compared to 0.850 g/day. The consumption of LC- ω 3PUFA being very low in this population, the authors computed tertiles in the highest quartile. In this group of high consumers (representing 90th and 95th percentile, they showed that a LC- ω 3PUFA consumption \geq 0.850 g/day was associated with decreased risk (OR: 0.47 CI: 0.25–0.90), compared to an intake < 0.120 g/day. Experimental studies provide support and mechanistic hypotheses^(53,54). However data are as yet insufficient to draw firm conclusions.

Table 6. Omega 3 fatty acids and breast cancer risk (incidence): cohort studies

Author, year country	Subjects and methods	Exposure measurement	ALA*	ω 3 LC-PUFA*	EPA	DHA	Remarks
Thiebaut <i>et al.</i> , 2008 ⁽⁴⁰⁾ , France	Follow-up 8 years (mean) 1650/56,007	Self-administered FFQ, 208 items	H (med 0.56% TEI) vs L (0.32) 1.05 (0.90, 1.23) T:0.62 From vegetable oil: H (med 0.70.% TEI) vs L (0.07) 0.87 (0.71–0.97 T: 0.017) From processed food H (med 0.128% TEI) vs L (0.00) 1.17, (1.01-.36) T:0.004	H (med 0.40% TEI) vs L (0.08) 0.94 (0.80, 1.10) T: 0.25			
Shannon <i>et al.</i> , 2007 ⁽⁴¹⁾ , China	322 cases/1030 controls nested in a BC screening cohort	Erythrocyte membranes FA	H (>0.32% TFA) vs L (≤0.18) 0.99 (0.54, 1.82)		H (>0.69% TFA vs L ≤0.46) 0.45 (0.26–0.77) T: 0.003	DHA (H > 5.46%TFA vs L ≤4.40) 0.61(0.36–1.04) T: 0.09	n-3PUFAs/n-6PUFAs, (H > 0.31 vs L ≤ 0.24) 0.66 (0.38–1.15) T: 0.16
Witt <i>et al.</i> , 2009 ⁽⁴²⁾ , Dk	Cases 463/1098 nested in 27520	Fatty acids measurement of adipose tissue		H (0.87–2.22% TFA) vs L (0.15–0.47) 0.96 (0.64–1.43)	H (0.13–0.30% TFA) vs L (0.02–0.06) 0.84 (0.58–1.23)	H (0.38–1.37% TFA) vs L (0.04–0.19) 1.08 (0.73–1.58)	DPA H (0.35–0.63% TFA) vs L (0.08–0.21)
Brasky <i>et al.</i> , 2010 ⁽⁴³⁾ , USA	VITAL cohort 819/35016 Post-Mnp Follow-up 6 years	Validated FFQ 120 items with question on supplements		Fish oil current user 0.68 (0.50–0.92) T:0.02			Ductal carcinoma: 0.68 (0.50–0.92) Lobular: NS Local tumor: 0.57 (0.38–0.84) Regional/distant: NS ER + 0.57 (0.38–0.84) PR + 0.63 (0.43–0.92) ER-, PR-NS
Murff <i>et al.</i> , 2011 ⁽⁴³⁾ , China	712/72571 Follow-up 8 years	Validated FFQ	H (med 1.39 g/d) vs L (0.63) 1.07 (0.76–1.50) T NS	H (med 0.20 g/d) vs L (0.02) 0.74 (0.52–1.06) T: NS			ω 6/ω 3 NS stratification:

RR (CI): relative risk (confidence interval); ALA, alpha-linolenic acid; omega 3 LC-PUFA, omega3 long chain-polyunsaturated fatty acids;; FFQ, food frequency questionnaire; H, highest quantile; L, lowest quantile; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; TEI, total energy intake; BC, breast cancer; TFA, total fatty acids; Mnp, menopausal.

For *gastric cancer*, a Japanese case-control study⁽⁵⁵⁾ (179 cases and 532 hospital-based controls) showed also a reduced risk (OR: 0.39, CI: 0.23–0.68, T: <0.005) associated with LC- ω 3PUFA consumption (>7.98% vs <5.61% of fatty acids in erythrocytes membranes).

Relationship to the incidence of *lung cancer* was not recently investigated. A rather old prospective cohort study⁽⁵⁶⁾ in Norway (153 cases/25,956 men and 25,496 women aged 16–56 years) showed an inverse association with intake of cod liver oil supplement (RR: 0.5, CI: 0.3–1.0).

Indeed, because of the anti-inflammatory, apoptotic and oxidative effects of LC- ω 3PUFA shown in cell cultures and in animal models^(26,48,57–59) more studies were conducted exploring the possible use of LC- ω 3PUFA as adjuvant therapy.

LC- ω 3PUFA as adjuvant in anti-cancer therapy

Several experimental *in vitro* and *in vivo* studies, demonstrated that omega 3 fatty acids sensitize tumour cells to effects of anticancer drugs in culture or in tumor-bearing animals^(60–62). Because of these first observations in animal models, a phase II trial⁽⁶³⁾ was undertaken on 25 patients with metastatic breast cancer, treated 3 times/day with 600 mg of DHA from algae origin, 7 to 10 days as a loading period before chemotherapy and during the 5 months of chemotherapy. As for a phase II protocol, there was no control group, but it was observed that patients DHA plasma levels presented a Gaussian distribution, reflecting a different ability to incorporate DHA. When stratifying the patients on the median of plasma levels (2.5%), it could be observed that the overall survival was significantly greater in the patients group showing plasma level >2.5% with a median survival time of 34 months vs 18 months in the patients showing plasma level <2.5% group ($p = 0.007$). This is an indication of the beneficial effect of DHA on chemotherapy treatment, however it has to be confirmed in a randomised controlled trial.

With regard to EPA, the Cochrane review published in 2007, covering the randomised controlled trials up to February 2005 concluded that there were 'insufficient data to establish whether oral EPA was better than placebo. Comparisons of EPA combined with a protein energy supplementation versus a protein energy supplementation (without EPA) in the presence of an appetite stimulant provided no evidence that EPA improves symptoms associated with the cachexia syndrome often seen in patients with advanced cancer⁽⁶⁴⁾.

A multicenter double-blind, randomised placebo controlled trial was conducted on 518 weight-losing patients with advanced gastrointestinal or lung cancer⁽⁶⁵⁾. Patients received a novel preparation of pure EPA at a dose of 2 g or 4 g daily or placebo (2 g EPA, $n = 175$; 4 g EPA, $n = 172$; placebo, $n = 171$). Patients were assessed at 4 weeks and 8 weeks. The best results were obtained in the 2 g EPA group, with a borderline significance ($p = 0.066$) for weight gain at 8 weeks (mean weight gain 1.2 kg, CI, 0.0 kg to 2.3 kg) compared with placebo. Physical function improved by approximately 7%

compared with placebo in those receiving 2 g EPA ($p = 0.04$) and fell by around 5% in those receiving 4 g EPA. Thus, there was no evidence of a dose response beyond 2 g per day, and if anything a suggestion of either a plateau or at worst a degree of deterioration with 4 g per day. However, in this study, EPA was given alone and not in combination with oral nutritional supplements.

The effects of an oral nutritional supplement containing omega 3 fatty acids on nutritional status and inflammatory markers were investigated in 40 patients with non-small cell lung cancer (NSCLC) stage III undergoing multimodality treatment in a double-blind, randomised, placebo controlled trial⁽⁶⁶⁾. The intervention patients showed a higher energy intake and a better weight maintenance than the control group (intention to treat basis, $p = 0.02$ at 4 weeks, and $p = 0.04$ at 8 weeks).

Other recent studies by a Canadian group aimed at analysing the effect of EPA on patients with non small cell lung cancer (NSCLC), especially with regard to the muscle mass. They first reported on the use of Computed tomography (CT) images to measure muscle mass and illustrate the relationship of muscle mass amount with serum fatty acids⁽⁶⁷⁾. Initially they followed about 600 solid lung tumours with longitudinal CT. In a first subset of 41 patients with lung cancer receiving chemotherapy, 25 were sarcopenic. Omega3 fatty acids were the only fatty acids to be different between the sarcopenic and the non sarcopenic, and patients with the maximal muscle loss presented the lowest concentration of omega3 fatty acids ($p = 0.005$). An open-label study with a contemporaneous control group was reported later⁽⁶⁸⁾: 40 patients who were receiving first-line chemotherapy (platinum-based doublet chemotherapy with either curative or palliative intent) consented to participate in a nutritional intervention study: 14 patients received 2.2 g EPA (I) and 16 the standard of care regimen (C); a reference group ($n = 104$) was established to ensure the representativity of the I and C groups. The primary endpoint was change in muscle mass between baseline and the end of chemotherapy. Adipose tissue, body weight, and plasma EPA at baseline and at the end of chemotherapy were secondary endpoints. Patients in the C group experienced an average weight loss of 2.3 ± 0.9 kg whereas I patients maintained their weight (0.5 ± 1.0 kg) ($p = 0.05$). Patients with the greatest increase in plasma EPA concentration after fish supplementation were found to have the greatest gains in muscle mass ($r^2: 0.55$, $p = 0.01$). Approximately 69% of I patients gained or maintained muscle mass vs 29% of C patients who, overall, lost 1 kg of muscle. Another subset of patients with a clinical diagnosis of stage IIIB or IV NSCLC, who were receiving first-line chemotherapy (platinum-based doublet chemotherapy with palliative intent) was enrolled in a study⁽⁶⁹⁾ designed as the one described above⁽⁶⁸⁾. The primary endpoint was chemotherapy response rates. Clinical benefit, chemotherapy toxicity, and survival were secondary endpoints. Sixty % of the I group had a increased response rate to chemotherapy vs 26% of the C group ($p = 0.008$) and a greater clinical benefit (80% vs 42%, $p = 0.02$). Toxicity did not differ, and one-year survival tend to be more frequent (60.0% vs 38.7%; $p = 0.15$).



Thus, limited evidence suggests that supplementation of fish oil of patients with NSCLC is beneficial.

General conclusion

The recent studies reported here did not increase the consistency of the results and do not permit to draw firm conclusions, except for ALA, which, probably, is neither a risk factor nor a beneficial factor with regards to cancers.

Thus, these new studies do not permit to go much further than the conclusion of the FAO/OMS⁽⁴⁾: observational studies only provided limited evidence on the possible role of LC- ω 3PUFA for colon cancer prevention. The same level of heterogeneity is observed for prostate cancer. The evidence is somewhat stronger for breast cancer when the exposure is as high as in Asian countries.

An interesting point is that 2 of these epidemiological studies^(13,29) brought about data in agreement with the mechanistic hypotheses developed by experimental data^(26,47,53), thereby increasing the biologic plausibility of the beneficial anti-inflammatory effect of LC- ω 3PUFA on cancers.

Another point is the evocation of explanations for heterogeneity: In addition to the inherent difficulties associated with epidemiology (measurement error, relevance of biomarkers, genetic polymorphism, cancer stages), the review of these recent the studies calls the attention on confounding: confounding with nutrients of other foods (essentially meat products for colorectal⁽¹⁶⁾, or processed food for breast cancer⁽⁴⁰⁾). The same can be hypothesised in the case of meat and dairy products for prostate cancers. Beyond a nutrient or a food, a favourable dietary pattern might confound the relationship between LC- ω 3PUFA and cancers as suggested by the frequent homogeneity in favourable results of Asian studies^(9,11,15,37–39,41).

Thus, nutritional recommendation will focus on fish consumption, or even better on a healthy dietary pattern, traditional Asian or Mediterranean.

With regard to cancer cachexia, inflammation and accompanying cytokines appear to be at the heart of the situation. Knowing the anti-inflammatory activity of LC- ω 3PUFA, their role as adjuvant, in view of the latest RCT on lung cancers, might be considered as of possible use, even if other RCT on other cancers still need to be undertaken, especially in breast cancers with regard to the possible beneficial effect on the chemotherapy outcome⁽⁶³⁾.

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