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 (ω3 PUFA). Fish intake is often described as part of a beneficial dietary pattern. However, observational epidemiological studies on the relationship between ω3 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 ω3 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 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-ω3PUFA 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-ω3PUFA 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 (ω3 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 ω3 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 ω3 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 ω3 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)
when they existed 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 ω3 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 ω3 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 ω3 PUFA**

The 3 case-control studies(9–11) showed a decreased risk associated with the highest quantile of LC-ω3 PUFA 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) study reporting no effect, one(17) an increased risk, and 3(14–15) reporting a reduced risk. One of these 3 studies(15), a subgroup of the Physician Health Study(11) 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 ω3 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 *PARK* 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Subjects and methods</th>
<th>Exposure measurement</th>
<th>ALA*</th>
<th>Omega 3 LC-PUFA* (g/day)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimura et al. 2007, Japan</td>
<td>782 CRC 793 population-based controls</td>
<td>FFQ by interview, 148 items</td>
<td></td>
<td>H (3.94) vs L (1.99)</td>
<td>0.74 (0.52–1.06) T: 0.05</td>
</tr>
<tr>
<td>Theodoratou et al. 2007, UK, Scotland</td>
<td>1455 CRC 1455 population-based controls M/F</td>
<td>Self-administered FFQ, 150 items</td>
<td>0.97 (0.76–1.24)</td>
<td>0.02 (0.01–0.05) T: 0.002</td>
<td></td>
</tr>
<tr>
<td>Kim et al. 2010, USA</td>
<td>White: 716 CC /787 Black: 213 CC/156 population-based controls</td>
<td>NIH diet history Questionnaire by interview, 124 items</td>
<td></td>
<td>0.97 (0.76–1.24)</td>
<td>0.02 (0.01–0.05) T: 0.002</td>
</tr>
</tbody>
</table>

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 quintile; L, lowest quintile; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; T, trend; NIH, National Institute of Health.
Table 2. Omega 3 fatty acids and colorectal cancer risk (incidence): prospective studies

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Subjects and methods</th>
<th>Exposure measurement</th>
<th>ALA*</th>
<th>ω-3 LC-PUFA*</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weijenberg et al., 2007, Netherlands</td>
<td>401 CC:130 CR/120852 Follow-up: 7.3 years</td>
<td>Validated FFQ, 150 items Database TRANSFAIR</td>
<td>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)</td>
<td>H: (6.67%TFA) vs (3.95) 0.60; (0.32–1.11) T = 0.10 EPA and DHA: NS</td>
<td>M without aspirin: ω-3 LC PUFA: 0.34 (0.15–0.82) T: 0.06 interaction 0.04 M with aspirin 1:09 (0.48–2.50). RR # for CC and RC Limits of quartiles not given</td>
</tr>
<tr>
<td>Hall et al., 2007, USA</td>
<td>Men 178 CR/282 41 controls nested in the Physician Health Study Follow-up up to 13 years</td>
<td>Total blood FA</td>
<td>Database TRANSFAIR</td>
<td>0.76 (0.59–0.98) T:0.02</td>
<td>In the multivariate model controlling for meat EPA 1.38 (1.02–1.85) T:NS</td>
</tr>
<tr>
<td>Hall et al., 2008, USA</td>
<td>500 CRC /21,406 the Physician Health Study Follow-up 22 y</td>
<td>Short FFQ + sea-food consumption Validation Adi-pose issue EPA + DHA</td>
<td>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 (0.68–1.57) T NS</td>
<td>F: NS</td>
<td>M invasive, proximal CC: H (med 0.770 g/D vs L 0.160) 0.27 (0.11–0.66) T:0.05 DHA: NS W: NS</td>
</tr>
<tr>
<td>Sasazuki et al., 2009 Japan</td>
<td>1268 CCR/98,466 M: 521 CC, 253 RC; F: 350 CC, 144 RC Follow-up 9-3 years</td>
<td>Validated FFQ, 138 items EPA, DPA and DHA summarized as marine n-3 PUFA</td>
<td>g/day H (≥1.19) vs L (&lt;0.78) 1:46 (1.09–1.95) T:0.04</td>
<td>0.94 (0.72–1.24)</td>
<td>In the multivariate model controlling for meat EPA 1.38 (1.02–1.85) T:NS</td>
</tr>
<tr>
<td>Daniel et al., 2009, USA</td>
<td>Follow-up 6 years 869 CCR (452 M, 417 F)/99,080 (43,108 M, 55,972 F)</td>
<td>Validated FFQ, 152 items</td>
<td>g/day H (≥0.24 g/d) vs L (&lt;0.10) 0.94 (0.72–1.24)</td>
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<tr>
<td>Butler et al., 2009, Singapore</td>
<td>Follow-up 9.8 years CCR 961,61321 Chinese</td>
<td>Validated FFQ, 165 items, 14 sea-food items</td>
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</table>

* 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, docosahaxaenoic acid; TFA, total fatty acids; T, trend; NS, non significant.

Breast cancer is the most common cancer in women worldwide. Hormone metabolism is the predominant influence factor for BC. High estradiol, either from endogenous sources, or, in parthenogenic women, becomes a risk factor for BC. The correlation between hormone levels and BC risk is not straightforward. Breast cancer is a multifactorial disease, and hormonal factors are only one of the risk factors. The relationship between hormone levels and BC risk has been extensively studied, and the results have been inconsistent. The relationship between hormone levels and BC risk is complex and influenced by many factors, including genetic, lifestyle, environmental, and other factors. Therefore, it is difficult to establish a clear correlation between hormone levels and BC risk.

Breast cancer is a complex disease that is influenced by multiple factors, including genetic, lifestyle, environmental, and other factors. The role of hormone levels in breast cancer risk is not straightforward, and the relationship between hormone levels and BC risk has been inconsistent. The biological plausibility from experimental studies, supporting a negative association between hormone levels and BC risk, is not strong enough to explain the overall pattern of results. It is likely that the relationship between hormone levels and BC risk is influenced by other factors, including genetic, lifestyle, and environmental factors. Therefore, it is difficult to establish a clear correlation between hormone levels and BC risk.

The biological plausibility from experimental studies (25,36), expressing an inverse association of hormone levels and BC risk, is not strong enough to explain the overall pattern of results. It is likely that the relationship between hormone levels and BC risk is influenced by other factors, including genetic, lifestyle, and environmental factors. Therefore, it is difficult to establish a clear correlation between hormone levels and BC risk.
Table 3. Omega 3 fatty acids and prostate cancer risk (incidence): case-control studies

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Subjects and methods</th>
<th>Exposure measurement</th>
<th>ALA*</th>
<th>ω 3 LC-PUFA*</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fradet et al. (29), 2009, USA</td>
<td>466 cases, 478 matched hospital based controls</td>
<td>Validated FFQ</td>
<td>H (2.55 g/d) vs L (0.79) 0.81 (0.48−1.35) T: 0.11</td>
<td>H (0.588 g/d) vs L (0.067) 0.37 (0.25−54) T: &lt;0.0001</td>
<td>Subjects with rs464310 (+8897 A&gt;G) SNP in COX-2: interaction: ( p = 0.02 ) stratification on consumption of ω 3 LC-PUFA H (0.588 g/d) vs L (0.067 g/d) 0.61 (0.46−0.81) T &lt;0.0001</td>
</tr>
<tr>
<td>Shannon et al. (30), 2010, USA</td>
<td>127 cases, 185 hospital-based screen PSA negative controls</td>
<td>Erythrocytes fatty acids</td>
<td>H, (&gt;0.135 % TFA) vs L (&lt;0.107) 0.72 (0.41−1.28) T: 0.112 (0.64−1.96) T: NS</td>
<td>EPA H (&gt;0.47 % TFA) vs L (0.35) 1.12 (0.64−1.96) T: NS</td>
<td>DHA: H (&gt;3.67 %) vs L (&lt;2.93) 1.06 (0.48−2.32) T: NS</td>
</tr>
</tbody>
</table>

OR (CI): estimated relative risk (confidence interval); ALA, alpha-linolenic acid; omega 3 LC-PUFA, omega 3 long chain polyunsaturated fatty acids; FFQ, 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.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Subjects and methods</th>
<th>Exposure measurement</th>
<th>ALA* (0·98–1·29)</th>
<th>ω-3 LC-PUFA* (0·98–1·29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giovanucci et al. (31), 2007, USA</td>
<td>Follow-up 15 years 3544 cases/47750 localized: 2161 advanced 523 fatal: 312</td>
<td>Validated self-administered FFQ 131 items</td>
<td>1·57 (1·19–2·07)</td>
<td>1·53 (1·07–2·02)</td>
</tr>
<tr>
<td>Park et al. (32), 2007 USA</td>
<td>Multiethnic 4404/82483 advanced 1278 Follow-up 8 years</td>
<td>Validated, self-administered FFQ 180 items</td>
<td>H median (1·01 g/1000 kcal) vs L (0·55) 0·92 (0·84–1·02)</td>
<td>0·89 (0·74–1·00) all Caucasians cases: 0·70 (0·64–0·99) T = 0·06 Hispanics: 0·83 (0·67–1·01) T = 0·03</td>
</tr>
<tr>
<td>Wallström et al. (33), 2007 Sweden</td>
<td>Follow-up 11 years 817/10564 advanced: 281</td>
<td>Interview-based, combined 7-day menu-book and FFQ 168-items</td>
<td>H med. (1·4 g/d vs L (2·7) 0·92 (0·73–1·15)</td>
<td>H med (0·44/d vs L (0·03) 1·28 (1·02–1·61) T:0·07</td>
</tr>
<tr>
<td>Chavarro et al. (34), 2007 USA</td>
<td>Follow-up 13 years 476 case/476 matched controls nested in PHS cohort 289 localized cases 130 cases Gleason ≥ 7 209 non aggressive tumors 108 advanced cases</td>
<td>blood</td>
<td>H (0·54 % TFA) vs L (0·24) 1·31 (0·89–1·95) T NS</td>
<td>H (0·70 % TFA) vs L (3·66) 0·62 (0·41–0·96) T:0·03</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Subjects</th>
<th>Exposure assessment</th>
<th>Analytical methods</th>
<th>EPA</th>
<th>DHA</th>
<th>ALA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuriki et al. (2007), Japan</td>
<td>103 cases/309 controls (all hospital-based)</td>
<td>Validated FFQ</td>
<td>Interview</td>
<td>H (≥0.39 TFA %) vs L (&lt;0.36 TFA %)</td>
<td>H (≥3.46 TFA %) vs L (&lt;3.79 TFA %)</td>
<td>H (≥4.79 TFA %) vs L (&lt;3.92 TFA %)</td>
</tr>
<tr>
<td>Kim et al. (2009), South Korea</td>
<td>200 women with breast cancer, 241 women with fibroadenoma</td>
<td>Validated FFQ</td>
<td>Interview + Membranes</td>
<td>H (≥0.56 g/100 kcal) vs L (&lt;0.48 g/100 kcal)</td>
<td>H (≥0.39 g/100 kcal) vs L (&lt;0.36 g/100 kcal)</td>
<td>H (≥1.39 g/100 kcal) vs L (&lt;1.26 g/100 kcal)</td>
</tr>
<tr>
<td>Pre-Mp (210/196)</td>
<td>Post-Mp (148/164)</td>
<td>104 items</td>
<td>213 items</td>
<td>0·38 (0·26–0·50) T: 0·010</td>
<td>0·51 (0·27–0·94) T: 0·003</td>
<td>0·69 (0·40–0·98) T: 0·007</td>
</tr>
</tbody>
</table>

*ALA is alpha-linolenic acid; omega 3 LC-PUFA, omega-3 long chain polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FFQ, food frequency questionnaire.

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. 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 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.

Thus, there is increasing evidence suggesting an association between BC and LC ω3 PUFAs, 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 showing an association between LC-ω3 PUFAs 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 fatty acids. One study compared the level of ALA and LC-ω3 PUFA 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) 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, 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 (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 ≥ 1·4 g/day compared to < 0·850 g/day. The consumption of LC-ω3PUFA 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-ω3PUFA consumption ≥ 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. However, data are as yet insufficient to draw firm conclusions.
Table 6. Omega 3 fatty acids and breast cancer risk (incidence): cohort studies

<table>
<thead>
<tr>
<th>Author, year country</th>
<th>Subjects and methods</th>
<th>Exposure measurement</th>
<th>ALA*</th>
<th>ω-3 LC-PUFA*</th>
<th>EPA</th>
<th>DHA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiebaut et al., 2008(40), France</td>
<td>Follow-up 8 years (mean) 1650/56,007</td>
<td>Self-administered FFQ, 208 items</td>
<td>H (med 0.56 % TEI) vs L (0.32) 1.05 (0.90, 1.23) T:0.02 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 (0.02) 1.17, (1.01–3.6) T:0.004</td>
<td>H (med 0.40 % TEI) vs L (0.08) 0.94 (0.80, 1.10) T: 0.25</td>
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<tr>
<td>Shannon et al., 2002(41), China</td>
<td>322 cases/1030 controls nested in a BC screening cohort</td>
<td>Erythrocyte membranes FA</td>
<td>H (&gt;0.32 % TFA) vs L (≤0.18) 0.89 (0.54, 1.32)</td>
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<tr>
<td>Witt et al., 2009(42), DK</td>
<td>Cases 463/1098 nested in 27520</td>
<td>Fatty acids measurement of adipose tissue</td>
<td>H (0.87–2.22 % TFA) vs L (0.15–0.47) 0.96 (0.64–1.43)</td>
<td>DHA (H &gt; 5.46 %TFA vs L ≤ 4.40) 0.61(0.36–1.04) T: 0.09</td>
<td>DPA H (0.35–0.63 % TFA) vs L (0.08–0.21)</td>
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<tr>
<td>Brasky et al., 2010(43), USA</td>
<td>VITAL cohort 819/35016 Post-Mnp Follow-up 6 years</td>
<td>Validated FFQ</td>
<td>Fish oil current user 0.68 (0.50–0.92) T:0.02</td>
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<td></td>
</tr>
<tr>
<td>Murff et al., 2011(44), China</td>
<td>712/72571 Follow-up 8 years</td>
<td>Validated FFQ</td>
<td>H (med 1.39 g/d) vs L (0.63) 1.07 (0.76–1.55) T NS</td>
<td>H (med 0.20 g/d) vs L (0.02) 0.74 (0.52–1.06) T: NS</td>
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</tbody>
</table>

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-\(\omega 3\) PUFA consumption \((>7·98 \% \text{< 5·61} \% \text{of fatty acids in erythrocytes membranes})\).

Relationship to the incidence of **lung cancer** was not recently investigated. A rather old prospective cohort study\(^{(56)}\) in Norway \((153 \text{ cases/25,956 men and 25,496 women aged 16-56 years})\) showed an inverse association with intake of cod liver oil supplement \((\text{RR}: 0·5; \text{CI: 0·3-1·0})\).

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

### LC-\(\omega 3\)PUFA 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 \((\text{without EPA})\) 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 \((2 g \text{ EPA, n 175}; 4 g \text{ EPA, n 172}; \text{placebo, n 171})\). Patients were assessed at 4 weeks and 8 weeks. The best results were obtained in the 2 g EPA group, with a borderline significance \((p = 0·006)\) for weight gain at 8 weeks \((\text{mean weight gain 1·2kg, CI, 0·0kg to 2·3kg})\) 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 \((\text{NSCLC})\) 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 \((\text{intention to treat basis, } p = 0·02 \text{ at 4 weeks, and } p = 0·04 \text{ at 8 weeks})\).

Other recent studies by a Canadian group aimed at analysing the effect of EPA on patients with non small cell lung cancer \((\text{NSCLC})\), especially with regard to the muscle mass. They first reported on the use of Computed tomography \((\text{CT})\) 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 \(\text{CT}\). 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 \((\text{platinum-based doublet chemotherapy with either curative or palliative intent})\) consented to participate in a nutritional intervention study: 14 patients received 2·2 g EPA \((1)\) 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 \((\text{platinum-based doublet chemotherapy with palliative intent})\) 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 \((80% \text{ vs 42%}, p = 0·02)\). Toxicity did no differ, and one-year survival tend to be more frequent \((60-0% \text{ vs 38-7%}, p = 0·15)\).
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(13): observational studies only provided limited evidence on the possible role of LC-ω3PUFA 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 benefits of the anti-inflammatory effect of LC-ω3PUFA 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 studies calls the attention on confounding: confounding with nutriments of other foods (essentially meat and dairy products for prostate cancers). Beyond a nutritional point of view, another risk factor might be considered as of possible use, even if other RCT studies(14,16) call for fruitful discussion on the topic. There are neither conflicts of interest nor funding.

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