

## Review

# Consumption of fish and omega-3 fatty acid and cancer risk: an umbrella review of meta-analyses of observational studies

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**Short running head:** Fish and omega-3 fatty acid intake and cancer risk

## **Abstract**

**Background:** There are multiple studies that have suggested the positive association between omega-3 fatty acid intake and the risk of cancer, however, there is a need to summarize and validate the evidence of the associations.

**Objective:** We aimed to summarize and evaluate the evidence for the association between omega-3 fatty acid intake and cancer outcomes.

**Design:** We searched PubMed from inception to December 1st, 2018 to conduct an umbrella review on meta-analyses of observational studies (cohort and case-control studies) that examined associations between omega-3 fatty acid intake and cancer risk (gastrointestinal, hepatobiliary, breast, gynecologic, prostate and brain/lung/skin). We determined the level of evidence of associations between omega-3 intake and the risk of the cancers.

**Results:** We initially screened 598 articles, and 15 reviews with 52 meta-analyses were included. Among 52 meta-analyses, 13 reported statistically significant results, but no meta-analysis showed a convincing or suggestive evidence of an association. While one meta-analysis on skin cancer (n=1 of 3) was not assessible for determining the evidence, the other 12 significant meta-analyses showed a weak evidence of omega-3 fatty acid intake and hepatobiliary cancer (n=4 of 6), breast cancer (n=3 of 14), prostate cancer (n=2 of 11) and brain tumor (n=2 of 2).

**Conclusion:** Although omega-3 fatty acids have been studied in several number of meta-analyses with regard to a wide range of cancer outcomes, only weak associations were identified in some cancer types with several limitations. In conclusion, we found limited evidence of protective effect of omega-3 fatty acid intake on cancer risk.

**Keywords:** Omega-3 fatty acid; cancer; umbrella review; meta-analysis

## **Introduction**

Omega-3 fatty acids, also called n-3 fatty acids, play important roles in human health and a variety of diseases [1], and therefore, they are considered as one of the important resources for the human body. Omega-3 fatty acids include long-chain alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) [2]. ALA is considered as an essential fatty acid because it cannot be synthesized by the body and must be obtained by consumption of food or supplements. However, as EPA and DHA are generated from ALA in the body, they are not considered as such [3]. Omega-3 fatty acids can be ingested from plant oil obtained from walnuts, flaxseed, and canola containing ALA [4]. EPA and DHA can be supplemented by eating fatty fish such as albacore tuna, salmon, mackerel, sardines, and herring [5]. Omega-3 fatty acids are incorporated in numerous parts of the body [6]. For example, DHA is a key component of all cell membranes [7] and EPA and DHA are precursors of metabolites that act as lipid mediators, assumed to be effective in preventing or treating several diseases [8].

The putative effects of omega-3 fatty acid supplementation on various cancer risks have been examined in numerous meta-analyses [9, 10]. However, these reviews have generated conflicting results and did not comprehensively appraise and consider biases and uncertainty in the body of the evidence to claim associations. In fact, hints biases have been identified in previous meta-research studies on cancer etiology. Recently, a new approach called umbrella review have been developed to investigate field wide evidence on complex topic such as cardiovascular diseases, cancers, and multiple health outcomes [11-13]. To the best of our knowledge, no umbrella review has investigated the association between omega-3 and cancer risk.

Given the aforementioned, we set out to provide an overview and evaluate the validity of reported associations of omega-3 fatty acids with various cancer risks, we performed the first

umbrella review of the evidence across existing systematic reviews and meta-analyses of observational studies.

## **Materials and Methods**

### *Search strategy of the literatures*

We performed an umbrella review of the systematic reviews and meta-analyses on associations between omega-3 fatty acid intake and cancer risks. Three investigators (J.I.S., H.J.S. and E.K.C.) searched PubMed database and included the articles that have been published in English only. The last search was done on December 1st. We used the following search terms: (omega 3 fatty acid OR n-3 fatty acid OR w-3 fatty acid OR  $\alpha$ -linolenic acid OR eicosapentaenoic acid (EPA) OR docosahexaenoic acid (DHA) OR polyunsaturated fatty acid (PUFA) OR docosapentaenoic acid (DPA) OR long chain polyunsaturated fatty acids (LCPUFA) OR fish OR fish oil OR krill oil) AND meta. We also excluded the articles by examining titles, abstracts, and full texts in order.

### *Eligibility and inclusion/exclusion criteria*

We included only systematic review and meta-analyses that examined the association between omega-3 fatty acid and cancer risk. We excluded studies that (1) examined genetic polymorphisms related to omega-3 fatty acid metabolism; (2) had omega-3 fatty acid status as the outcome; (3) dealt with cost-effectiveness of omega-3 fatty acid supplementation; (4) meta-analyses in which the treatment arm contained several compounds including omega-3 fatty acids; (5) meta-analyses focusing on the ratio of omega-3/ omega-6 PUFA; (6) not reporting cancer risk; (7) meta-analyses not about omega-3 fatty acids. We also excluded meta-

regression analyses and sensitivity analyses. A detailed flow chart of screening and selection processes of eligible articles is presented in Figure 1.

#### *Extraction of the data*

Data were extracted by 3 investigators (G.K., H.P. and E.J.) and any discrepancy was discussed and resolved by consensus. For each eligible review, we gathered the outcome data of meta-analyses. We also abstracted and recorded the name of first authors, journal, publication year, type of outcome, types of patients, study design (cohort and/or case-control), the number of studies, type of metric (risk ratio, odds ratio and hazard ratio, as reported by the authors of the meta-analysis), effect size with the corresponding confidence intervals, meta-analysis model (fixed/random),  $p$ -value for overall effects,  $I^2$  or  $\chi^2$  for between-study heterogeneity,  $p$ -value for between-study heterogeneity and Egger's  $p$ -value or other statistics for publication bias.

#### *Statistical re-analyses of the meta-analyses with statistically significant result under conventional criteria ( $p < 0.05$ )*

With the extracted data from meta-analyses, we re-analyzed the meta-analyses showing statistically significant results ( $p < 0.05$ ). We collected all the included individual studies and performed the re-analysis using the software package Comprehensive Meta-Analysis (v.3.3.070). Then, we summarized different summary effect sizes with the corresponding 95% confidence intervals (CIs) from the results of meta-analyses. We applied random-effects models by assuming that individual effects of studies were different (i.e. between-study heterogeneity). We also calculated the 95% prediction interval (PI), which further accounts for



between-study heterogeneity and evaluates the uncertainty of the effect that would be expected in a new study addressing the same association [14-16].

We then assessed the heterogeneity between studies using  $I^2$ , which ranges from 0 to 100%, and the  $p$ -value of the  $\chi^2$ -based Cochran Q test [17].  $I^2$  is the ratio of between-study variance over the sum of the within-study and between-study variance [18].  $I^2$  values >50% or >75% are usually interpreted as having large or very large heterogeneity, respectively [18]. We also evaluated small-study effects to identify whether such studies tend to give much larger risk estimates than large studies [19]. By using the regression asymmetry test proposed by Egger and colleagues, we assessed small-study effects indicating publication and other reporting bias [20]. An Egger  $p$ -value of less than 0.10 in a random-effects model was judged to provide evidence for small-study effects.

#### *Level of evidence of associations*

Based on results of our re-analysis of statistically significant meta-analysis, we further grouped the associations between omega-3 fatty acids and cancer risks according to the conventional criteria [17, 21]: evidence of strong statistical significance using random-effects meta-analyses at  $p$ -value<0.01 (a threshold that has been suggested to substantially reduce the number of false positive findings) [22-24], magnitude of between-study heterogeneity ( $I^2$  <50%), number of cases with binary outcomes > 1,000, absence of small study effects (Egger  $p$ -value  $\geq$  0.10) and 95% PI excluded the null.

**Non-significant** associations had  $p$ -value >0.05.

**Weak** evidence in which there is a large heterogeneity ( $I^2$ >50%) or publication bias and evidence of small-study effects. Even though there is no large heterogeneity ( $I^2$ >50%) or

publication bias, small number of cases (number of cases<1,000) or a nominally significant association ( $p= 0.01-0.05$ ) would be observed.

**Suggestive** evidence required a significant association with  $p$ -value<0.01, the absence of large heterogeneity ( $I^2<50\%$ ), absence of publication bias, 95% PI included the null, number of cases>1,000, and no evidence of small-study effects. If all other criteria except number of cases or total participants were satisfied, we classified the group as suggestive evidence.

**Convincing** evidence required strong statistical significance in a meta-analysis with  $p$ -value<0.01, the absence of large heterogeneity ( $I^2<50\%$ ), no evidence for publication bias, number of cases with binary outcomes>1,000, no evidence of small-study effects, and 95% PI excluded the null.

If a meta-analysis included only one study, the between-study heterogeneity and Egger  $p$ -value was not available. In this case, we determined the level was not assessable (NA).

## **Results**

### *Overall summary of meta-analyses*

Total of 598 articles were initially reviewed with exclusions of duplicated ones, and 15 eligible articles with 52 meta-analyses were included in our review. We systematically categorized 52 meta-analyses into 6 cancer risk categories as follows: gastrointestinal cancer, hepatobiliary cancer, breast cancer, gynecologic cancer, prostate cancer and brain/lung/skin cancer [9, 25-38]. There were no eligible meta-analyses articles on leukemia, lymphoma, or hematologic malignancy.

### *Gastrointestinal cancer outcomes*

Among 4 meta-analyses identified from the literature search, all showed a statistically non-significant association of cancer risk with omega-3 fatty acids intake. The studies were on gastric cancer (n=1) and colorectal cancer (n=3) (Table 1).

#### *Hepatobiliary cancer outcomes*

Six meta-analyses examined hepatobiliary-related. Among these, four meta-analyses were statistically significant, with reduction of cancer incidence with omega-3 fatty acids intake. The other 2 results were not statistically significant (Table 2).

#### *Breast cancer outcomes*

Among 14 meta-analyses, 3 showed a statistically significant result for reduction of breast cancer risk with omega-3 fatty acids intake. The remaining meta-analyses showed no association (Table 3).

#### *Gynecologic cancer outcomes*

Among 10 meta-analyses, omega-3 fatty acids intake did not affect the incidence of ovarian cancer (n=5) or endometrial cancer (n=5) (Table 4).

#### *Prostate cancer outcomes*

Among 11 meta-analyses, three meta-analysis showed statistically significant results on association with risk of prostate cancer with omega-3 fatty acids intake (n=3). Of 3 results, one

meta-analysis showed that consumption of long chain n-3 increased the risk of prostate cancer (RR 1.14, 95% CI 1.01-1.28), whereas the other two meta-analyses found a protective effective of omega-3 intake. The remaining meta-analyses reported no association (n=8) (Table 5).

#### *Brain/lung/skin cancer outcomes*

Among 7 meta-analyses associated with brain, lung and skin cancer, three reported statistically significant associations. Two studies revealed a significant reduced incidence of brain tumors with omega-3 fatty acids intake (n=2 of 2). Also, a meta-analysis including one case-control study found a reduced risk of melanoma significantly. Contrary to the results above, there was no association between the role of omega-3 fatty acids in lung (n=2) and other skin cancer (n=2) (Table 6).

#### *Levels of evidence of association*

Of 13 significant associations, 12 studies were available to determine the level of evidence. One study on melanoma was not assessable since it contained only one individual study. Of 12 associations, no study showed a convincing or suggestive evidence of association. All meta-analyses with significance showed a weak evidence: hepatobiliary cancer (n=4 of 6), breast cancer (n=3 of 14), prostate cancer (n=3 of 11) and brain tumor (n=2 of 2). One meta-analysis showed statistically significant result, but the level of evidence was not applicable due to lack of included studies. The other 39 meta-analyses were non-significant.

Among 12 meta-analyses with weak level of evidence, five (41.7%) had a nominally significant association ( $p=0.01-0.05$ ). Four (33.3%) had  $I^2>50\%$ , implying large heterogeneity between studies, however, none of them showed very large heterogeneity ( $I^2>75\%$ ). Regarding

publication bias, seven studies (58.3%) showed evidence of small study effects (Egger  $p$ -value  $< 0.10$ ). (Table 7)

## **Discussion**

Our umbrella review is the first to examine the evidence from meta-analyses of observational studies on the relationship between omega-3 fatty acid intake and cancer risk. Extensive data were provided by 15 eligible meta-analyses. Among these, we extracted meta-analyses for primary or secondary outcomes, classified these meta-analyses according to types of outcomes, and evaluated each type of analysis with level of significance, using collected data (e.g.,  $p$  for overall effect,  $p$  for heterogeneity, and  $I^2$ ,  $p$  for publication bias, prediction intervals and number of participants). As we classified the results into convincing, suggestive, weak, or non-significant evidence, all meta-analyses with significance showed a weak evidence, but no meta-analysis showed a convincing or suggestive evidence of an association. All 12 meta-analyses for the effects of omega 3 intake on hepatobiliary cancer (n=4 of 6), breast cancer (n=3 of 14), prostate cancer (n=3 of 11) and brain tumor (n=2 of 2) showed statistically significant results with a weak evidence. One meta-analysis on skin cancer was also significant, but it only contained a single individual study, and the level of evidence was not assessible. As noted above, although some types of cancers showed that omega-3 intake may reduce the incidence or risk, the level of evidence was weak. Regarding the sources of omega 3 fatty acid, the studies were on total dietary fish intake (n=12, 23.1%), PUFA (n=18, 34.6%), ALA (n=9, 17.3%), EPA (n=5, 9.6%), DHA (n=4, 7.7%) and DPA (n=3, 5.8%). This means that the sources of omega 3 intake are not a significant factor in cancer risk.

One study stated that there was a positive association between long-chain n-3 intake and risk of prostate cancer. However, it only included 2 individual cohorts, with *p*-value showing nominal significance ( $p=0.036$ ), which should be interpreted cautiously.

Our results found that few studies on omega-3 intake showed high levels of evidence. Thus, it will be important not to overemphasize the claimed associations by clarifying the evidence.

Most clinicians focus only on the overall *p*-value to determine the significance of results. However, we should also consider the effect size, 95% CI, heterogeneity, publication bias, or funnel plot data [18, 19, 39]. Using a method that follows the conventional criteria, it is possible to establish the level of evidence much easily for multiple meta-analyses.

An umbrella review is a type of meta-analysis designed to provide a conclusive summary of reports highlighting the level of evidence [40]. Since Ioannidis et al. first suggested the concept in 2009 [41], an increasing number of umbrella reviews have been published [41]. A single meta-analysis usually offers the misuse of inadequate statistical methods [41] and can result in misleading outcomes, distortion, and bias. Recently, the level of evidence has gained more importance to increase the value of the publication and provide an informative summary for decision makers in healthcare [40, 41].

Most of the meta-analyses primarily presented their results with random- or fixed-effects size and 95% CI (with *p*-value). However, in order to determine the noteworthiness of the results, it was important to conduct further analysis of between-study heterogeneity and small study effects [17, 20].

Previously published meta-analyses mostly had a lack of information about publication bias, which made it difficult to assess the validity of the evidence synthesis [42]. In our study, 24 of 52 meta-analyses did not mention the value for publication bias, which include three

statistically significant results. This limitation explains the need to comprehensively interpret the meta-analyses using an umbrella review.

The public considers omega-3 fatty acids to be beneficial for health, leading to the consumption of fish oil supplements. Reflecting this trend, much research has assessed the potential association of omega-3 fatty acids with health outcomes, with a special focus on reduction, which led to conflicting results. Nevertheless, no comprehensive study on omega-3 fatty acids has specifically studied levels of evidence. Moreover, most recent evidence from a randomized controlled trial highlighted that supplementation with omega-3 fatty acids did not significantly lower the incidence of cancer, which supports our finding [10].

In addition, we compared our final result with the report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR). According to the latest report published from Continuous Update Project (CUP) initiated by WCRF/AICR, high amounts of fish consumption was significantly associated with reduction of liver and colorectal cancer, both graded as 'limited – suggestive' evidence [43]. However, studies of the other cancers including head and neck, lung, stomach, pancreas, gallbladder, ovary, endometrium, prostate, kidney, bladder and skin cancer draw a conclusion with 'limited-no conclusion' evidence. In our study, the meta-analyses assessing the risk of colorectal cancer were not significant, however, in case of liver cancer, there were a positive association supported by a weak level of evidence. Putatively, omega-3 fatty acids have an anti-inflammatory, which may lower risk for cancers, including liver and colorectal cancer [44, 45]. Nevertheless, the level of evidence was still limited, suggesting that the further studies are needed to confirm these findings. The lack of strong evidences regarding HCC may be partly explained also by the multifactorial etiology of such tumor type. Indeed, it may be possible that relevant biological differences in response to omega-3 fatty acid may exist in case of viruses-related neoplasms vs. HCC associated to peculiar environmental risk factors vs. others.

The mechanisms of cancer preventive effect of omega-3 fatty acids remain to be elucidated. There has been evidence for their effect on the immune system. An epidemiological study has shown that marine omega-3 fatty acids are associated with lower risk of colorectal cancer containing higher numbers of FOXP3+ regulatory T cells [46], corroborated by in vitro experimental evidence for their stimulating effect on CD4+ T cells via suppressing regulatory T cells [46].

In fact, one of possible reasons why there is only weak evidence for effects of omega-3 fatty acids on overall organ-specific cancer risk is combining biologically heterogeneous cancer subtypes into one entity, which has been done in a vast majority of epidemiological studies. When there is a causal association only with a specific cancer subtype, an effect size is always larger for the specific subtype than for overall cancer containing all subtypes [47, 48]. Weak or no evidence for risks of overall organ-specific cancers does not exclude causal associations for specific cancer subtypes [47, 48].

There were some limitations in our study. First, we included studies from certain published meta-analyses and thus might have missed some individual studies if they were not identified with our pre-defined systematic search strategy. Second, we did not reanalyze all the data. Third, an original epidemiological study could be cited in two or more meta-analyses. Even though one meta-analysis that has better quality should be selected for one cause-response association and meta-analyses should be summarized in one-exposure-many-outcomes, or many-exposures-one-outcome associations in forest plots, small study numbers could not fully reflect these facts. Fourth, the degree or definitions of high or low omega-3 intake may across individual studies. Finally, we only investigated only the association of omega-3 intake on cancer risks. Further meta-research articles on a level or ratio of omega 3 fatty acid components or cancer mortality need to be explored in the future studies.



## **Conclusion**

In conclusion, although omega-3 fatty acids are commonly used as dietary supplements and many studies on omega-3 fatty acids have been published, there was no convincing evidence related to the effects of omega-3 fatty acids on cancer risk. Weak evidence supported the association between omega-3 fatty acids and breast cancer, hepatocellular carcinoma, prostate cancer, and brain tumor. The conclusion of no convincing evidence is limited to omega-3 uptake, not on mortalities or levels or ratios of omega-3: omega-6. For outcomes with suggestive or weak evidence, further studies are needed to identify the actual effects of omega-3 fatty acids on cancer risks by individual patient data meta-analyses. In addition, subgroup analyses according to various factors, as well as elimination of bias and errors in big data or original meta-analyses, are clearly warranted.

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**Table 1.** Summary of the meta-analyses of omega-3 fatty acids and gastrointestinal cancer risk

| <u>Author(vear)</u><br><u>Outcome</u> | <u>No. of</u><br><u>studies</u> | <u>Type of</u><br><u>studies</u> | <u>Type of omega-3 intake</u>            | <u>Cases/total</u><br><u>participants</u> | <u>Type of</u><br><u>metrics</u> | <u>Summary</u><br><u>effect size (95%</u><br><u>CI)</u> | <u>Model</u> | <u>P-value</u> | <u>I<sup>2</sup> (P-value)</u> | <u>Egger</u><br><u>(P-value)</u> | <u>Statistically</u><br><u>significance</u> |
|---------------------------------------|---------------------------------|----------------------------------|--|---|----------------------------------|---|--------------|----------------|--------------------------------|----------------------------------|---|
| <u>Wu (2011)</u>                      |                                 |                                  |  |   |                                  |   |              |                |                                |                                  |   |
| Gastric cancer                        | 17                              | CC,<br>Cohort                    | High fish consumption                    | 5323/136226                               | RR                               | 0.87 (0.71, 1.07)                                       | Random       | NR             | 73.3 (<0.001)                  | 0.59                             | No  |
| <u>Shen (2012)</u>                    |                                 |                                  |  |   |                                  |   |              |                |                                |                                  |   |
| Colorectal cancer                     | 7                               | Cohort                           | High ω -3 PUFAs intake                   | 4656/489465                               | RR                               | 0.97 (0.86, 1.10)                                       | Random       | NR             | 38.1 (0.08)                    | NR                               | No  |
| <u>Chen (2015)</u>                    |                                 |                                  |  |   |                                  |   |              |                |                                |                                  |   |
| Colorectal cancer                     | 11                              | CC,<br>Cohort                    | Marine n-3 PUFA intake (high<br>vs. low) | NR  | RR                               | 1.00 (0.93, 1.07)                                       | Random       | NR             | 0.0 (0.51)                     | 0.73                             | No  |
| <u>Geelen (2007)</u>                  |                                 |                                  |  |   |                                  |   |              |                |                                |                                  |   |
| Colorectal cancer                     | 14                              | Cohort                           | Fish consumption (high vs. low)          | NR  | RR                               | 0.88 (0.78, 1.00)                                       | Random       | NR             | 18.3 (0.25)                    | 0.66                             | No  |

Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; CC, case-control; RR, risk ratio; ω, omega; NR, not reported; PUFAs, polyunsaturated fatty acids

**Table 2.** Summary of the meta-analyses of omega-3 fatty acids and hepatobiliary cancer risk

| <u>Author(year)</u><br>Outcome | No. of studies | Type of studies | Type of omega-3 intake | Cases/total participants | Type of metrics | Summary effect size (95% CI) | Model  | P-value | I <sup>2</sup> (P-value) | Egger (P-value) | Statistically significance |
|--------------------------------|----------------|-----------------|------------------------|--------------------------|-----------------|------------------------------|--------|---------|--------------------------|-----------------|----------------------------|
| <u>Huang (2015)</u>            |                |                 |                        |                          |                 |                              |        |         |                          |                 |                            |
| HCC                            | 10             | CC, Cohort      | High total fish intake | 1984/5370040             | RR              | 0.82 (0.71, 0.94)            | Random | 0.018   | 12.8 (0.325)             | 0.07            | Yes                        |
| HCC                            | 5              | CC              | High total fish intake | 809/10352                | RR              | 0.79 (0.59, 1.06)            | Random | 0.27    | 41.9 (0.142)             | NR              | No                         |
| HCC                            | 5              | Cohort          | High total fish intake | 1175/5359688             | RR              | 0.82 (0.70, 0.96)            | Random | 0.011   | 0.0 (0.487)              | NR              | Yes                        |
| <u>Gao (2015)</u>              |                |                 |                        |                          |                 |                              |        |         |                          |                 |                            |
| HCC                            | 11             | Nest CC, Cohort | Fish consumption       | NR/1196005               | RR              | 0.65 (0.51, 0.79)            | Random | NR      | 44.1 (0.057)             | <0.01           | Yes                        |
| HCC                            | 2              | Cohort, CC      | n-3 PUFA intake        | 583/91291                | RR              | 0.49 (0.19, 0.79)            | Random | NR      | 0.0 (0.929)              | NA              | Yes                        |
| HCC                            | 2              | Cohort, CC      | ALA intake             | 583/91291                | RR              | 0.70 (0.30, 1.10)            | Random | NR      | 0.0 (1.000)              | NA              | No                         |

Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; RR, risk ratio; CC, case-control; HCC, hepatocellular carcinoma; ALA, alpha-linolenic acid; PUFAs, polyunsaturated fatty acids; NR, not reported; NA, not assessible

**Table 3.** Summary of the meta-analyses of omega-3 fatty acids and breast cancer risk

| Author(year)<br>Outcome | No. of<br>studies | Type of<br>studies        | Type of omega-3 intake  | Cases/total<br>participants | Type of<br>metrics | Summary<br>effect size (95%<br>CI) | Model  | P-value | I <sup>2</sup> (P-value) | Egger<br>(P-value) | Statistically<br>significance |
|-------------------------|-------------------|---------------------------|---|-----------------------------|--------------------|------------------------------------|--------|---------|--------------------------|--------------------|-------------------------------|
| <u>Zheng (2013)</u>     |                   |                           |   |                             |                    |                                    |        |         |                          |                    |                               |
| Breast cancer           | 19                | Nest CC,<br>CC,<br>Cohort | Highest marine n-3 PUFA<br>intake                             | 16178/527392                | RR                 | 0.86 (0.78, 0.94)                  | Random | NR      | 54 (0.003)               | 0.017              | Yes                           |
| Breast cancer           | 10                | Nest CC,<br>Cohort        | Total n-3 PUFA  | NR                          | RR                 | 0.96 (0.86, 1.06)                  | Random | NR      | 13 (NR)                  | 0.04               | No                            |
| Breast cancer           | 11                | CC,<br>Cohort             | Marine n-3 PUFA(Diet)   | 11519/443619                | RR                 | 0.85 (0.76, 0.96)                  | Random | NR      | 67 (0.001)               | NR                 | Yes                           |
| Breast cancer           | 3                 | Cohort                    | Per 0.1g/day increment of<br>dietary marine n-3 PUFA          | 3114/117488                 | RR                 | 0.95 (0.90, 1.00)                  | Random | NR      | 52 (0.1)                 | NR                 | Yes                           |
| Breast cancer           | 6                 | Cohort                    | Per 0.1% energy increment of<br>daily dietary marine n-3 PUFA | 6344/288626                 | RR                 | 0.95 (0.90, 1.00)                  | Random | NR      | 79 (<0.001)              | NR                 | No                            |
| Breast cancer           | 14                | Nest CC,<br>CC,<br>Cohort | Highest dietary fish intake                                   | 13323/687770                | RR                 | 1.03 (0.93, 1.14)                  | Random | NR      | 54 (0.009)               | 0.6                | No                            |
| Breast cancer           | 14                | Nest CC,<br>Cohort        | Per 15g/day increment of fish<br>intake                       | 13323/666400                | RR                 | 1.00 (0.97, 1.03)                  | Random | NR      | 64.0 (0.001)             | NR                 | No                            |
| Breast cancer           | 11                | Nest CC,<br>CC,<br>Cohort | Marine n-3 fatty (EPA)  | NR                          | RR                 | 0.93 (0.85, 1.02)                  | Random | NR      | 2.9 (NR)                 | NR                 | No                            |
| Breast cancer           | 11                | Nest CC,<br>CC,<br>Cohort | Marine n-3 fatty (DHA)  | NR                          | RR                 | 0.88 (0.75, 1.03)                  | Random | NR      | 37.6 (NR)                | NR                 | No                            |
| Breast cancer           | 5                 | Nest CC,<br>CC,<br>Cohort | Marine n-3 fatty (DPA)  | 4746/284724                 | RR                 | 0.90 (0.69, 1.19)                  | Random | NR      | 0.0 (NR)                 | NR                 | No                            |
| Breast cancer           | 6                 | CC,<br>Cohort             | ALA(Diet)   | 8274/281756                 | RR                 | 0.98 (0.90, 1.06)                  | Random | NR      | 5.1 (0.384)              | NR                 | No                            |
| Breast cancer           | 4                 | CC,<br>Cohort             | Per 0.1g/day increment of<br>dietary ALA intake               | 6310/190451                 | RR                 | 0.99 (0.98, 1.01)                  | Random | NR      | 65.0 (0.035)             | NR                 | No                            |
| Breast cancer           | 3                 | Cohort                    | Per 0.1% energy increment of<br>daily dietary ALA intake      | 5510/171680                 | RR                 | 1.00 (0.99, 1.00)                  | Random | NR      | 0.0 (0.770)              | NR                 | No                            |
| Breast cancer           | 12                | Nest CC,<br>CC,<br>Cohort | ALA (Tissue biomarker and<br>Diet)                            | 9296/284724                 | RR                 | 0.97 (0.90, 1.04)                  | Random | NR      | 0.0 (0.548)              | 0.37               | No                            |

Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; CC, case-control; RR, risk ratio; NR, not reported; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acids; PUFAs, polyunsaturated fatty acids; DPA, docosapentaenoic acid



**Table 4.** Summary of the meta-analyses of omega-3 fatty acids and gynecologic cancer risk

| <u>Author(vear)</u><br><u>Outcome</u>  | <u>No. of</u><br><u>studies</u> | <u>Type of</u><br><u>studies</u> | <u>Type of omega-3 intake</u>                 | <u>Cases/total</u><br><u>participants</u> | <u>Type of</u><br><u>metrics</u> | <u>Summary</u><br><u>effect size (95%</u><br><u>CI)</u> | <u>Model</u> | <u>P-value</u> | <u>I<sup>2</sup> (P-value)</u> | <u>Egger</u><br><u>(P-value)</u> | <u>Statistically</u><br><u>significance</u> |
|--|---------------------------------|----------------------------------|---|---|----------------------------------|---|--------------|----------------|--------------------------------|----------------------------------|---|
| <u>Hoang (2018)</u>  |                                 |                                  |   |   |                                  |   |              |                |                                |                                  |   |
| Endometrial cancer   | 5                               | CC,<br>Cohort                    | Dietary omega-3 fatty acids<br>(high vs. low) | NR/159907                                 | OR/HR                            | 0.95 (0.72, 1.26)                                       | Random       | NR             | 67.3 (NR)                      | NR                               | No  |
| Endometrial cancer   | 4                               | CC,<br>Cohort                    | EPA intake (high vs. low)                     | NR /158999                                | OR/HR                            | 0.86 (0.58, 1.30)                                       | Random       | NR             | 81.3 (NR)                      | NR                               | No  |
| Endometrial cancer   | 5                               | CC,<br>Cohort                    | ALA intake (high vs. low)                     | NR /159907                                | OR/HR                            | 0.93 (0.81, 1.08)                                       | Random       | NR             | 0.0 (NR)                       | NR                               | No  |
| Endometrial cancer   | 4                               | CC,<br>Cohort                    | DHA intake (high vs. low)                     | NR /158999                                | OR/HR                            | 0.89 (0.63, 1.28)                                       | Random       | NR             | 76.1 (NR)                      | NR                               | No  |
| Endometrial cancer   | 2                               | CC,<br>Cohort                    | DPA intake (high vs. low)                     | NR /88774                                 | OR/HR                            | 0.86 (0.71, 1.03)                                       | Random       | NR             | 0.0 (NR)                       | NA                               | No  |
| Ovarian cancer   | 3                               | CC                               | Dietary omega-3 fatty acids<br>(high vs. low) | 4269/5803                                 | OR                               | 0.79 (0.61-1.03)  | Random       | NR             | 74.5 (NR)                      | NR                               | No  |
| Ovarian cancer   | 2                               | CC                               | EPA intake (high vs. low)                     | 3238/3392                                 | OR                               | 0.89 (0.73, 1.08)                                       | Random       | NR             | 71.5 (NR)                      | NA                               | No  |
| Ovarian cancer   | 3                               | CC                               | ALA intake (high vs. low)                     | 4269/5803                                 | OR                               | 0.99 (0.77, 1.26)                                       | Random       | NR             | 58.6 (NR)                      | NR                               | No  |
| Ovarian cancer   | 2                               | CC                               | DHA intake (high vs. low)                     | 3238/3392                                 | OR                               | 0.91 (0.75, 1.11)                                       | Random       | NR             | 0.0 (NR)                       | NA                               | No  |
| Ovarian cancer   | 1                               | CC                               | DPA intake (high vs. low)                     | 1366/1414                                 | OR                               | 1.06 (0.85, 1.33)                                       | NA           | NR             | NA                             | NA                               | No  |
| Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; OR, odds ratio; HR, hazard ratio; NR, not reported; CC, case-control; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acids; DPA, docosapentaenoic acid; NA, not assessible |                                 |                                  |   |   |                                  |   |              |                |                                |                                  |   |

**Table 5.** Summary of the meta-analyses of omega-3 fatty acids and prostate cancer risk

| <u>Author(year)</u><br><u>Outcome</u>   | <u>No. of studies</u> | <u>Type of studies</u> | <u>Type of omega-3 intake</u>        | <u>Cases/total participants</u> | <u>Type of metrics</u> | <u>Summary effect size (95% CI)</u> | <u>Model</u> | <u>P-value</u> | <u>I<sup>2</sup> (P-value)</u> | <u>Egger (P-value)</u> | <u>Statistically significance</u> |
|---|-----------------------|------------------------|--------------------------------------|---------------------------------|------------------------|-------------------------------------|--------------|----------------|--------------------------------|------------------------|-----------------------------------|
| <u>Fu (2015)</u>  |                       |                        |                                      |                                 |                        |                                     |              |                |                                |                        |                                   |
| Prostate cancer   | 5                     | Nest CC, CC, Cohort    | Per 0.5g/day increase in ALA intake  | 7781/430090                     | RR                     | 0.99 (0.98, 1.00)                   | Random       | -NR            | 0.0 (0.670)                    | NR                     | Yes                               |
| Prostate cancer   | 5                     | Nest CC, CC, Cohort    | Per 0.05g/day increase in EPA intake | 7778/450999                     | RR                     | 1.02 (0.99, 1.05)                   | Random       | NR             | 36.1 (0.181)                   | NR                     | No                                |
| <u>Szymanski (2010)</u>   |                       |                        |                                      |                                 |                        |                                     |              |                |                                |                        |                                   |
| Prostate cancer   | 12                    | CC                     | High fish consumption                | 5777/9805                       | OR                     | 0.85 (0.72, 1.00)                   | Random       | 0.05           | 44 (0.05)                      | 0.62                   | No                                |
| Prostate cancer   | 12                    | Cohort                 | High fish consumption                | 13924/445820                    | RR                     | 1.01 (0.90, 1.14)                   | Random       | 0.83           | 59 (0.005)                     | 0.84                   | No                                |
| <u>Alexander (2015)</u>   |                       |                        |                                      |                                 |                        |                                     |              |                |                                |                        |                                   |
| Prostate cancer   | 13                    | Cohort                 | High ω-3 PUFA intake (Diet)          | NR/446243                       | SRRE                   | 1.00 (0.93, 1.09)                   | Random       | NR             | 50.4 (0.019)                   | NR                     | No                                |
| <u>Chua (2012)</u>  |                       |                        |                                      |                                 |                        |                                     |              |                |                                |                        |                                   |
| Prostate cancer   | 4                     | Cohort                 | ALA intake                           | NR/177133                       | RR                     | 0.92 (0.85, 0.99)                   | Random       | 0.019          | 0 (0.677)                      | 0.34                   | Yes                               |
| Prostate cancer   | 2                     | Cohort                 | Total omega 3 intake                 | NR /93047                       | RR                     | 0.97 (0.89, 1.07)                   | Random       | 0.549          | 20 (0.264)                     | NR                     | No                                |
| Prostate cancer   | 3                     | Cohort                 | EPA intake                           | NR /151326                      | RR                     | 1.05 (0.96, 1.15)                   | Random       | 0.317          | 41 (0.182)                     | 0.65                   | No                                |
| Prostate cancer   | 3                     | Cohort                 | DHA intake                           | NR /196192                      | RR                     | 1.03 (0.94, 1.13)                   | Random       | 0.489          | 52 (0.127)                     | 0.54                   | No                                |
| Prostate cancer   | 2                     | Cohort                 | Long-chain n-3                       | NR /30731                       | RR                     | 1.14 (1.01, 1.28)                   | Random       | 0.036          | 25 (0.249)                     | NA                     | Yes                               |
| Prostate cancer   | 4                     | Cohort                 | Long-chain n-3 +(DHA+EPA)            | NR /82483                       | RR                     | 1.03 (0.97, 1.10)                   | Random       | 0.278          | 0 (0.462)                      | 0.51                   | No                                |
| Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; CC, case-control; OR, odds ratio; RR, risk ratio; SRRE, summary relative risk estimates; NR, not reported; NA, not assessable; ω, omega; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acids; PUFAs, polyunsaturated fatty acids |                       |                        |                                      |                                 |                        |                                     |              |                |                                |                        |                                   |

**Table 6.** Summary of the meta-analyses of omega-3 fatty acids and brain/lung/skin cancer risk

| <u>Author(vear)<br/>Outcome</u>   | <u>No. of<br/>studies</u> | <u>Type of<br/>studies</u> | <u>Type of omega-3 intake</u>          | <u>Cases/total<br/>participants</u> | <u>Type of<br/>metrics</u> | <u>Summary<br/>effect size (95%<br/>CI)</u> | <u>Model</u> | <u>P-value</u> | <u>I<sup>2</sup> (P-value)</u> | <u>Egger<br/>(P-value)</u> | <u>Statistically<br/>significance</u> |
|---|---------------------------|----------------------------|--|-------------------------------------|----------------------------|---|--------------|----------------|--------------------------------|----------------------------|---------------------------------------|
| <u>Lian (2017)</u>  |                           |                            |  |                                     |                            |   |              |                |                                |                            |                                       |
| Brain tumor   | 9                         | CC,<br>Cohort              | Fish intake (high vs. low)             | 4428/505296                         | RR                         | 0.83 (0.70, 0.99)                           | Random       | NR             | 37.5 (0.119)                   | 0.02                       | Yes                                   |
| Brain tumor   | 9                         | CC,<br>Cohort              | Per 100g/week increase fish<br>intakes | 4428/505296                         | RR                         | 0.95 (0.91, 0.98)                           | Random       | NR             | 51.7 (0.035)                   | 0.02                       | Yes                                   |
| <u>Zhang (2014)</u>   |                           |                            |  |                                     |                            |   |              |                |                                |                            |                                       |
| Lung cancer   | 11                        | Cohort                     | PUFA intake (high vs low)              | NR/1268442                          | RR                         | 0.91(0.78, 1.06)                            | Random       | 0.230          | 67.7 (0.001)                   | 0.186                      | No                                    |
| Lung cancer   | 11                        | Cohort                     | PUFA intake (per 5g/day<br>increment)  | NR/1268442                          | RR                         | 0.98 (0.96, 1.01)                           | Random       | 0.142          | 69.5 (<0.001)                  | 0.135                      | No                                    |
| <u>Noel (2014)</u>  |                           |                            |  |                                     |                            |   |              |                |                                |                            |                                       |
| Skin cancer, Basal cell<br>carcinoma  | 3                         | Cohort                     | n-3 PUFA intake (high vs. low)         | NR/44539                            | RR                         | 1.05 (0.86, 1.28)                           | Random       | NR             | 53.6 (0.14)                    | NR                         | No                                    |
| Skin cancer,<br>Squamous cell<br>carcinoma  | 2                         | CC,<br>Cohort              | n-3 PUFA intake (high vs. low)         | NR/1890                             | RR                         | 0.86 (0.59, 1.23)                           | Random       | NR             | 52.6 (0.15)                    | NA                         | No                                    |
| Skin cancer,<br>Melanoma  | 1                         | CC                         | n-3 PUFA intake (high vs. low)         | 304/609                             | OR                         | 0.52 (0.34, 0.78)                           | NA           | NR             | NA                             | NA                         | Yes                                   |
| Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; CC, case-control; OR, odds ratio; RR, risk ratio; NR, not reported; NA, not assessible; PUFA, polyunsaturated fatty acid |                           |                            |  |                                     |                            |   |              |                |                                |                            |                                       |

**Table 7.** Summary of 12 re-analyses of meta-analyses with statistically significant results

| Outcome          | Type of studies     | Type of intervention                              | No. of cases | Significance (random-effects) | Heterogeneity | Small study effects | Prediction interval | Evidence |
|------------------|---------------------|---|--------------|-------------------------------|---------------|---------------------|---------------------|----------|
| Liver cancer     | CC, Cohort          | High total fish intake                            | 1984         | <0.01                         | Not large     | Yes                 | Excluded null       | Weak     |
| Liver cancer     | Cohort              | High total fish intake                            | 1175         | <0.01                         | Not large     | Yes                 | Excluded null       | Weak     |
| HCC              | Nest CC, Cohort     | Fish consumption                                  | NR           | <0.01                         | Not large     | Yes                 | Included null       | Weak     |
| HCC              | CC, Cohort          | n-3 PUFA intake                                   | 583          | <0.05, but >0.01              | Not large     | NA                  | NA                  | Weak     |
| Breast cancer    | Nest CC, CC, Cohort | Highest marine n-3 PUFA intake                    | 16178        | <0.01                         | Large         | Yes                 | Included null       | Weak     |
| Breast cancer    | CC, Cohort          | Marine n-3 PUFA (Diet)                            | 11519        | <0.01                         | Large         | Yes                 | Included null       | Weak     |
| Breast cancer    | Cohort              | Per 0.1g/day increment of dietary marine n-3 PUFA | 3114         | <0.01                         | Large         | No                  | Included null       | Weak     |
| Prostate cancer  | Nest CC, CC, Cohort | Per 0.5g/day increase in ALA intakes              | 7781         | <0.05, but >0.01              | Not large     | No                  | Included null       | Weak     |
| Prostate cancer] | Cohort              | ALA intake  | NR           | <0.05, but >0.01              | Not large     | No                  | Included null       | Weak     |
| Prostate cancer  | Cohort              | Long-chain n-3                                    | NR           | <0.05, but >0.01              | Not large     | NA                  | NA                  | Weak     |
| Brain tumor      | CC, Cohort          | Fish intake (high vs. low)                        | 4428         | <0.05, but >0.01              | Not large     | Yes                 | Included null       | Weak     |
| Brain tumor      | CC, Cohort          | Per 100g/week increase fish intakes               | 4428         | <0.01                         | Large         | Yes                 | Included null       | Weak     |

Abbreviations: No., number; CC, case-control; HCC, hepatocellular carcinoma; PUFA, polyunsaturated fatty acid; ALA, alpha-linolenic acid; NR, not reported; NA, not assessible

## **Figure legends**

Figure 1. Flow chart of the literature search

