**Review Articles**

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

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**Abbreviation footnote: ALA,** alpha-linolenic acid; AMSTAR2, A Measurement Tool to Assess Systematic Review 2; CUP, continuous Update Project; DPA, Docosapentaenoic acid; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not assessable; PI, prediction interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WCRF/AICR, Word Cancer Research Fund/American Institute for Cancer Research.

**Abstract**

Multiple studies suggesting that omega-3 fatty acid intake may have a protective effect on cancer risk, however, its true association remain controversial. We performed an umbrella review of meta-analyses to summarize and evaluate the evidence for the association between omega-3 fatty acid intake and cancer outcomes. We searched PubMed, Embase, and the Cochrane Database of Systematic Reviews from inception to December 1, 2018. We included meta-analyses of observational studies that examined associations between fish or omega-3 fatty acid intake and cancer risk (gastrointestinal, liver, breast, gynecologic, prostate and brain, lung, skin) and determined the level of evidence of associations. In addition, we appraised the quality of the evidence of significant meta-analysis using Grading of Recommendations Assessment, Development and Evaluation system. We initially screened 598 articles, and 15 articles including 57 meta-analyses were eligible. Among 57 meta-analyses, 15 reported statistically significant results. We found that 12 meta-analyses showed weak evidence of an association between omega-3 fatty acid intake and cancer risk: liver cancer (n=4 of 6), breast cancer (n=3 of 14), prostate cancer (n=3 of 11) and brain tumor (n=2 of 2). The other three meta-analyses in endometrial cancer and skin cancer were not assessable for determining the evidence level. No meta-analysis showed a convincing, highly suggestive or suggestive evidence of an association. In the sensitivity analysis of meta-analyses by study design, we found weak association between omega-3 fatty acid intake and breast and brain cancer risk in cohort studies but no statistically significant association in case-control studies. Although omega-3 fatty acids have been studied in several meta-analyses with regard to a wide range of cancer outcomes, only weak associations were identified in some cancer types with several limitations. Considering the non-significant or weak evidence level, clinicians and researchers should cautiously interpret association between omega-3 fatty acid consumption and cancer risks.

**Keywords**: Omega-3 fatty acid, fish, 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), EPA, and DHA (2). ALA is considered 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).

Multiple animal studies and in-vitro studies have supported the protective effect of consumption of fish with high omega-3 fatty acid and cancer risk. Omega-3 fatty acids modulate the production of inflammatory signaling molecules, called eicosanoids, and regulate the inflammatory reaction along with the effect on cell growth (9). Succeeding epidemiological studies and meta-analyses also examined the putative effects of omega-3 fatty acid supplementation on various cancer (10, 11). However, these reviews have generated conflicting results and did not comprehensively appraised and considered biases and uncertainty in the body of the evidence to claim causal associations.

Recently, a new approach called umbrella review has been developed to investigate field-wide evidence on complex topics such as cardiovascular diseases, cancers, and multiple health outcomes (12-14). The number of meta-analyses in the field of medicine has increased exponentially, and the abundance of the results not always have positive effect on clinical decisions. Recently published meta-analyses, including those in nutrition, only give a limited perspective of results by examining specific intervention’s effect on specific outcome. Differences in types and doses of omega-3 fatty acid intake affects the conclusion in different types of cancer and led to contradictory and inconsistent findings in previously published meta-analyses (15). A systematical approach to provide evidence is thus needed.

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. To the best of our knowledge, no umbrella review has investigated the association between omega-3 and cancer risk.

Methods

This umbrella review of meta-analyses was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines (16).

Search strategy of the literature

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, Embase, and the Cochrane Database of Systematic Reviews and for articles that have been published in English only. The last search was done on December 1, 2018.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 EPA OR DHA OR PUFA OR docosapentaenoic acid (DPA) OR long chain PUFA OR fish OR fish oil OR krill oil) AND cancer AND meta. We screened for eligible articles by subsequently 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. We also excluded meta-regression analyses and sensitivity analyses. A detailed flow chart of the screening and selection process of eligible articles is presented in **Figure 1**.

Assessment of methodological quality

The methodological quality of the included systematic reviews and meta-analyses were evaluated using a Measurement Tool to Assess Systematic Reviews 2 (AMSTAR2) tool (17). This instrument is a 16-point assessment tool referrring methodological aspects of included studies, provides a rationale for item selecting, identifies critical domains to assess the validity of the results of the systematic reviews and meta-analyses. The classification of the validity follows as high, moderate, low, or critical low instead of using the overall score. The detailed results with rating criteria are shown in **Supplemental Table 1**.

Extraction of the data

Data were extracted by three 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 (RR, OR and HR, as reported by the authors of the meta-analysis), effect size with the corresponding 95% CIs, meta-analysis model (fixed/random), *p*-value for overall effects, *I2* or χ2 for between-study heterogeneity, *p*-value for between-study heterogeneity and Egger’s *p*-value or other statistics for publication bias.

Data analysis

With the extracted data from meta-analyses, we re-analyzed the eligible meta-analyses extracted from the previously publisehd studies. We collected all the included individual studies and performed re-analysis using the software package Comprehensive Meta-Analysis software version 3.3.070 (Biostat, NJ, USA). Then, we summarized different summary effect sizes with the corresponding 95% CI 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 (18-20).

We assessed the heterogeneity between studies using *I2*, which ranges from 0 to 100%, and the *p*-value of the χ2-based Cochran Q test (21). *I2*is the ratio of between-study variance over the sum of the within-study and between-study variance (22). *I2* values >50% or >75% are usually interpreted as having large or very large heterogeneity, respectively (22). We also evaluated small-study effects, also commonly known as publication bias, to identify whether such studies tend to give much larger risk estimates than large studies (23). By using the regression asymmetry test proposed by Egger and colleagues, we assessed small-study effects indicating publication and other reporting bias (24).An Egger *p*-value of less than 0.10 in a random-effects model was judged to provide evidence for small-study effects.

In addition, we assessed the presence of excess significance, a measure of literature bias that compares the expected versus the observed number of statistically significant studies in a meta-analysis (25). Excess significance was calculated as a ratio of the effect size of the largest individual study (the study with the smallest variance) in each meta-analysis to the summary effect size of the meta-analysis, with a ratio smaller than 1 indicating the presence of excess significance bias (26). For statistically significant meta-analyses, we also appraised the quality of the evidence from each meta-analysis using Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (27).

Level of evidence of associations

Based on results of our re-analysis of the eligible meta-analysis, we further grouped the associations between omega-3 fatty acids and cancer risks according to the criteria from conventional umbrella review (15, 28) with following components: evidence of strong statistical significance using random-effects meta-analyses at *p*-value<10-6, magnitude of between-study heterogeneity (*I2*<50%), number of cases with binary outcomes >1,000, absence of small study effects (Egger *p-*value≥0.10), 95% PI excluded the null.

**Convincing** evidence required strong statistical significance in a meta-analysis with *p*-value<10-6, the absence of large heterogeneity (*I2*<50%), number of cases with binary outcomes>1,000, no evidence of small-study effects (Egger *p*-value>0.10*)* and excess significance bias, and 95% PI excluded the null.

**Highly suggestive** evidence required a strong statistical significance with p-value<10-6, 95% PI included the null, the number of cases>1,000, the presence of large heterogeneity (*I2*>50%), small-study effects and excess significance bias.

**Suggestive** evidence required a significant association with *p*-value<0.001, 95% PI included the null, number of cases>1,000, the presence of large heterogeneity (*I2*>50%), small-study effects and excess significance bias.

**Weak** evidence in which there is a large heterogeneity (*I2*>50%) or publication bias and evidence of small-study effects. Even though there is no large heterogeneity (*I2*>50%) or publication bias or excess significance bias, a small number of cases (number of cases<1,000) or a nominally significant association (*p*= 0.001-0.05) would be observed.

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

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).

*Re-analysis of meta-analyses by study design*

We further processed the sensitivity analysis by study design. With the reported results from meta-analyses, including both case-control and cohort studies in a single analysis, we separated them by study design (case-control and cohort) and performed the re-analysis. Meta-analyses including only one cohort and case-control study, respectively, were not accounted for the sensitivity analysis. We then evaluated the level of evidence of the outcome from re-analysis.

Results

Overall summary of meta-analyses

A total of 598 articles were initially identified with exclusions of duplicated ones, and 15 eligible articles with 57 meta-analyses were included in our review. We systematically categorized 57 meta-analyses into six cancer risk categories as follows: gastrointestinal cancer, liver cancer, breast cancer, gynecologic cancer, prostate cancer and brain/lung/skin cancer (10, 29-42). Brain, lung, skin cancer was assessed in group due to small number of meta-analyses.

Gastrointestinal cancer outcomes

Among five meta-analyses identified from the literature search, all showed no association of cancer risk with omega-3 fatty acids intake. The studies were on gastric cancer (n=1) and colorectal cancer (n=4) (**Table 1**).

Liver cancer outcomes

Six meta-analyses associated with omega-3 fatty acids and liver cancer were identified. Among these, four meta-analyses were statistically significant, with reduction of cancer incidence with omega-3 fatty acid intake. The other two results presented no associations (**Table 2**).

Breast cancer outcomes

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

Gynecologic cancer outcomes

Among 14 meta-analyses, two meta-analyses found that high EPA and DHA intake significantly reduced the risk of ovarian cancer, respectively (EPA intake, OR 0.57, 95% CI 0.39-0.84; DHA intake, OR 0.64, 95% CI 0.44-0.94), however, they both only included one case-control study. Others did not affect the incidence of ovarian cancer (n=7) or endometrial cancer (n=5) (**Table 4**).

Prostate cancer outcomes

Among 11 meta-analyses, three meta-analyses showed statistically significant results for the association between omega-3 fatty acid intake and prostate cancer (n=3). Of three 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 effect of omega-3 intake. One study showed a marginally non-significant association between high consumption of fish and prostate cancer (*p*=0.05). The remaining meta-analyses reported no association (n=7) (**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 acid intake (n=2 of 2). Also, a meta-analysis consisted of one case-control study found a reduced risk of melanoma significantly. Contrary to the results above, there was no association between the omega-3 fatty acid intake in lung (n=2) and other skin cancer (n=2) (**Table 6**).

Levels of evidence of association

Out of 15 significant associations, 12 studies were available to determine the level of evidence (**Table 7**). Three meta-analyses on melanoma and breast cancer 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 statistically significant findings showed a weak evidence: liver 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 *I2*>50%, implying large heterogeneity between studies, however, none of them showed very large heterogeneity (*I2*>75%). Regarding publication bias, seven studies (58.3%) showed evidence of small study effects (Egger *p*-value< 0.10). In case of GRADE assessment, two meta-analyses on breast and prostate cancer were rated as moderate certainty and three on HCC and prostate cancer showed low certainty. The other seven meta-analyses were rated as very low certainty.

Out of 42 non-significant associations, 40 meta-analyses showed a non-significant level of evidence (*p*-value>0.05). One outcome of meta-analysis was unavailable for re-analysis due to insufficient information of individual studies used for meta-analysis. The other one study only included a single individual study, so the level of evidence was not assessible **(Table 8)**.

*Re-analysis of meta-analyses by study design*

Among 57 meta-analyses, 15 of them included both case-control and cohort studies in a single meta-analysis (Table 9). To investigate the highest marine n-3 fatty acid intake and its potential association with breast cancer, a weak level of evidence of a meta-analysis of observational studies and cohort studies was found, while analysis of case-control studies revealed no significance. Also, two studies of brain tumor showed weak level of evidence on both meta-analyses of observational studies and case-control studies; however, they were not significant in case of cohort studies. However, there was only one case-control study included in the pooled meta-analysis of observational studies, and thus it should be interpreted cautiously.

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 articles with 57 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 *I2*, *p* for publication bias, prediction intervals and number of participants). All 12 meta-analyses for the effects of omega-3 intake on liver 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. Three meta-analyses on endometrial cancer and skin cancer were also significant, but it only contained a single individual study, and the level of evidence was not assessable.

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

In this study, we not only focused on a specific type of omega-3 fatty acids but included the various types of omega-3 fatty acids. Conventional meta-analyses only focus on a single comparison with a single outcome, which is difficult to broadly understand a subject. To overcome this limitation, the goal of our umbrella review is to help clinicians and researchers an extensive understanding of the association, therefore we included different sources of omega-3 fatty acid in this study. Regarding the sources of omega-3 fatty acid, the studies were on total dietary fish intake (n=12, 21.1%), PUFA (n=18, 31.6%), ALA (n=10, 17.5%), EPA (n=6, 10.5%), DHA (n=5, 8.8%) and DPA (n=3, 5.3%).

In **Table 9**, we found out that high intake of marine n-3 PUFA significantly reduced the risk of breast cancer in both meta-analyses of observational studies and cohort studies, however, it was not significant in that of case-control studies (10). Despite the non-significant result from the meta-analysis of case-control studies, the direction of the outcomes was consistent between case-control and cohort studies. This is due to the included 11 cohort studies were designed to see the effect prospectively, therefore, it is considered to be more reliable. In contrast, in case of brain tumor, high consumption of fish showed a positive effect in the meta-analysis of both case-control and observational studies, however, it showed a negative effect in the cohort study design. Given these points, it is important to consider both meta-analyses of case-control and cohort studies respectively to draw the conclusions.

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 (22, 23, 43). 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 (44). Since Ioannidis et al. first suggested the concept in 2009, an increasing number of umbrella reviews have been published (45).A single meta-analysis usually offers the misuse of inadequate statistical methods (45) 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 (44, 45).

Most of the meta-analyses primarily presented their results with random- or fixed-effects size and 95% CI with *p*-value. However, to determine the noteworthiness of the results, it was important to conduct further analysis of between-study heterogeneity and small study effects (24, 46).

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 (47). In our study, 19 of 57 meta-analyses did not mention the value for publication bias, which include four 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 (11).

In addition, we compared our final result with the report from the Word 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 were significantly associated with reduction of liver and colorectal cancer incidence, both graded as ‘limited – suggestive’ evidence (48). 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 the case of liver cancer, there was a positive association supported by a weak level of evidence. Putatively, omega-3 fatty acids have anti-inflammatory effects, which may lower risk for cancers including liver and colorectal cancer (49, 50). Nevertheless, the level of evidence was still limited, suggesting that 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 with peculiar environmental risk factors vs. others.

The mechanisms of the cancer preventive effect of omega-3 fatty acids remain to be elucidated. There has been evidence for their effect on the immune system. A large prospective cohort 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 (51), corroborated by in vitro experimental evidence for their stimulating effect on CD4+ T cells via suppressing regulatory T cells (51).

In fact, one of the 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 (52, 53). Weak or no evidence for risks of overall organ-specific cancers does not exclude causal associations for specific cancer subtypes (52, 53).

There were some limitations in our study. First, we included studies from 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 observational 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 intake may across individual studies. Measurements defined in the meta-analyses varied across individual observational studies and consumption categories were not clear in some studies, which should lead to cautious interpretation. Finally, we only investigated 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 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. From the results separating the study design, we found that there was a discrepancy in the association with breast cancer and brain tumor. To draw the consistent outcome with high level of 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 warranted.

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All authors read and approved the final manuscript.

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

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & year, type of cancer** | ***n*1** | **Type of studies** | **Type of omega-3 fatty acid intake2** | **Cases/total participants** | **Type of metrics** | **Summary effect size (95% CI)** | **Model** | ***P*-value** | ***I2*(*P*-value)** | **Egger’s**  ***p*-value** | **Statistically significant** |
| Wu S et al., 2011 (41) |  |  |  |  |  |  |  |  |  |  |  |
| Gastric cancer | 17 | CC, Cohort | High fish consumption | 5323/136226 | RR | 0.87 (0.71, 1.07) | Random | NR | 73.3 (<0.001) | 0.59 | No |
| Shen X-J et al., 2012 (39) |  |  |  |  |  |  |  |  |  |  |  |
| 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 |
| Chen G-C et al., 2015 (30) |  |  |  |  |  |  |  |  |  |  |  |
| Colorectal cancer | 10 | CC, Cohort | Total n-3 PUFA intake (high vs. low) | 7372/581943 | RR | 0.99 (0.92, 1.06) | Random | NR | 10.5 (0.34) | 0.61 | No |
| Colorectal cancer | 11 | CC, Cohort | Marine n-3 PUFA intake (high vs. low) | NR | RR | 1.00 (0.93, 1.07) | Random | NR | 0.0 (0.51) | 0.73 | No |
| Geelen A et al., 2007 (34) |  |  |  |  |  |  |  |  |  |  |  |
| 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 |

1*n* represents the number of studies included in the meta-analysis.

2Definitions of comparison of each category follow that described in the original studies.

3CC, case control; NR, not reported.

**Table 2.** Summary of the meta-analyses of fish and omega-3 fatty acid intake and liver cancer risk

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & year, type of cancer** | ***n*1** | **Type of studies** | **Type of omega-3 fatty acid intake2** | **Cases/total participants** | **Type of metrics** | **Summary effect**  **size (95% CI)** | **Model** | ***P*-value** | ***I2*(*P*)** | **Egger’s**  ***p*-value** | **Statistically significant** |
| Huang R-X et al., 2015 (36) |  |  |  |  |  |  |  |  |  |  |  |
| 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 |
| Gao M et al., 2015 (33) |  |  |  |  |  |  |  |  |  |  |  |
| HCC | 11 | CC, Cohort | Fish consumption | NR/1196005 | RR | 0.65 (0.51, 0.79) | Random | NR | 44.1 (0.057) | <0.01 | Yes |
| HCC | 2 | CC, Cohort | n-3 PUFA intake | 583/91291 | RR | 0.49 (0.19, 0.79) | Random | NR | 0.0 (0.929) | NA | Yes |
| HCC | 2 | CC, Cohort | ALA intake | 583/91291 | RR | 0.70 (0.30, 1.10) | Random | NR | 0.0 (1.000) | NA | No |

1*n* represents the number of studies included in the meta-analysis.

2Definitions of comparison of each category follow that described in the original studies.

3ALA, alpha-linolenic acid; CC, case control; NR, not reported.

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

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & year, type of cancer** | ***n*1** | **Type of studies** | **Type of omega-3 fatty acid intake2** | **Cases/total participants** | **Type of metrics** | **Summary effect size (95% CI)** | **Model** | ***P*-value** | ***I2*(*P*-value)** | **Egger’s**  ***p*-value** | **Statistically significant** |
| Zheng J-S et al., 2013 (10) |  |  |  |  |  |  |  |  |  |  |  |
| Breast cancer | 17 | CC, Cohort | Highest marine n-3 PUFA intake | 16178/527392 | RR | 0.86 (0.78, 0.94) | Random | NR | 54 (0.003) | 0.017 | Yes |
| Breast cancer | 10 | CC, Cohort | Total n-3 PUFA | NR | RR | 0.96 (0.86, 1.06) | Random | NR | 13 (NR) | 0.04 | No |
| Breast cancer | 10 | 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 dietary marine n-3 PUFA | 3114/117488 | RR | 0.95 (0.90, 1.00) | Random | NR | 52 (0.1) | NR | Yes |
| Breast cancer | 5 | Cohort | Per 0.1% energy increment of daily dietary marine n-3 PUFA | 6344/288626 | RR | 0.95 (0.90, 1.00) | Random | NR | 79 (<0.001) | NR | No |
| Breast cancer | 11 | CC, Cohort | Highest dietary fish intake | 13323/687770 | RR | 1.03 (0.93, 1.14) | Random | NR | 54 (0.009) | 0.6 | No |
| Breast cancer | 11 | CC, Cohort | Per 15g/day increment of fish intake | 13323/666400 | RR | 1.00 (0.97, 1.03) | Random | NR | 64.0 (0.001) | NR | No |
| Breast cancer | 10 | CC, Cohort | Marine n-3 fatty (EPA) | NR | RR | 0.93 (0.85, 1.02) | Random | NR | 2.9 (NR) | NR | No |
| Breast cancer | 10 | CC, Cohort | Marine n-3 fatty (DHA) | NR | RR | 0.88 (0.75, 1.03) | Random | NR | 37.6 (NR) | NR | No |
| Breast cancer | 4 | CC, 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 | Cohort | ALA(Diet) | 8274/281756 | RR | 0.98 (0.90, 1.06) | Random | NR | 5.1 (0.384) | NR | No |
| Breast cancer | 4 | Cohort | Per 0.1g/day increment of 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 daily dietary ALA intake | 5510/171680 | RR | 1.00 (0.99, 1.00) | Random | NR | 0.0 (0.770) | NR | No |
| Breast cancer | 12 | CC, Cohort | ALA (Tissue biomarker and Diet) | 9296/284724 | RR | 0.97 (0.90, 1.04) | Random | NR | 0.0 (0.548) | 0.37 | No |

1*n* represents the number of studies included in the meta-analysis.

2Definitions of comparison of each category follow that described in the original studies.

3ALA, alpha-linolenic acid; CC, case control; DPA, docosapentaenoic acid; NR, not reported.

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

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & year, type of cancer** | ***n*1** | **Type of studies** | **Type of omega-3 fatty acid intake2** | **Cases/total participants** | **Type of metrics** | **Summary effect size (95% CI)** | **Model** | ***P*-value** | ***I2*(*P*-value)** | **Egger’s**  ***p*-value** | **Statistically significant** |
| Hoang T et al., 2018 (35) |  |  |  |  |  |  |  |  |  |  |  |
| Endometrial cancer | 2 | CC | Dietary omega-3 fatty acids (high vs. low) | 1010/2451 | OR | 0.87 (0.65, 1.18) | Random | 0.382 | 0.0 (0.351) | NA | No |
| Endometrial cancer | 3 | Cohort | Dietary omega-3 fatty acids (high vs. low) | NR/157456 | HR | 1.03 (0.63, 1.68) | Random | 0.902 | 81.0 (0.001) | 0.615 | No |
| Endometrial cancer | 1 | CC | EPA intake (high vs. low) | 556/1089 | OR | 0.57 (0.39, 0.84) | Random | NR | NA | NA | Yes |
| Endometrial cancer | 3 | Cohort | EPA intake (high vs. low) | NR/157456 | HR | 1.00 (0.61, 1.62) | Random | 0.10 | 81.7 (0.000) | 0.693 | No |
| Endometrial cancer | 2 | CC | ALA intake (high vs. low) | 1010/2451 | OR | 0.95 (0.72, 1.25) | Random | 0.709 | 0.0 (0.739) | NA | No |
| Endometrial cancer | 3 | Cohort | ALA intake (high vs. low) | NR/157456 | HR | 0.92 (0.76, 1.11) | Random | 0.368 | 0.0 (0.838) | 0.074 | No |
| Endometrial cancer | 1 | CC | DHA intake (high vs. low) | 556/1089 | OR | 0.64 (0.44, 0.94) | Random | NR | NA | NA | Yes |
| Endometrial cancer | 3 | Cohort | DHA intake (high vs. low) | NR/157456 | HR | 1.01 (0.63, 1.60) | Random | 0.981 | 79.2 (0.008) | 0.529 | No |
| Endometrial cancer | 2 | Cohort | DPA intake (high vs. low) | NR /88774 | HR | 0.86 (0.71, 1.03) | Random | NR | 0.0 (NR) | NA | No |
| Ovarian cancer | 3 | CC | Dietary omega-3 fatty acids (high vs. low) | 4269/5803 | OR | 0.79 (0.61-1.03) | Random | NR | 74.5 (NR) | NR | No |
| Ovarian cancer | 2 | CC, Cohort | 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, Cohort | 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, Cohort | 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 |

1*n* represents the number of studies included in the meta-analysis.

2Definitions of comparison of each category follow that described in the original studies.

3ALA, alpha-linolenic acid; CC, case control; DPA, docosapentaenoic acid; NA, not assessible; NR, not reported.

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

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & year, type of cancer** | ***n*1** | **Type of studies** | **Type of omega-3 fatty acid intake2** | **Cases/total participants** | **Type of metrics** | **Summary effect size (95% CI)** | **Model** | ***P*-value** | ***I2*(*P*-value)** | **Egger’s**  ***p*-value** | **Statistically significant** |
| Fu Y-Q et al., 2015 (32) |  |  |  |  |  |  |  |  |  |  |  |
| Prostate cancer | 5 | 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 | 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 |
| Szymanski KM et al., 2010 (40) |  |  |  |  |  |  |  |  |  |  |  |
| 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 |
| Alexander DD et al., 2015 (29) |  |  |  |  |  |  |  |  |  |  |  |
| 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 |
| Chua ME et al., 2012 (31) |  |  |  |  |  |  |  |  |  |  |  |
| 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 |

1*n* represents the number of studies included in the meta-analysis.

2Definitions of comparison of each category follow that described in the original studies.

3ALA, alpha-linolenic acid; CC, case control; NA, not assessible; NR, not reported.

**Table 6.** Summary of the meta-analyses of fish and omega-3 fatty acid intake and brain, lung, and skin cancer risk

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & year, type of cancer** | ***n*1** | **Type of studies** | **Type of omega-3 fatty acid intake2** | **Cases/total participants** | **Type of metrics** | **Summary effect size (95% CI)** | **Model** | ***P*-value** | ***I2*(*P*-value)** | **Egger’s**  ***p*-value** | **Statistically significant** |
| Lian W et al., 2017 (37) |  |  |  |  |  |  |  |  |  |  |  |
| Brain tumor | 9 | CC, 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, Cohort | Per 100g/week increase fish intakes | 4428/505296 | RR | 0.95 (0.91, 0.98) | Random | NR | 51.7 (0.035) | 0.02 | Yes |
| Zhang Y-F et al., 2014 (42) |  |  |  |  |  |  |  |  |  |  |  |
| 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 increment) | NR/1268442 | RR | 0.98 (0.96, 1.01) | Random | 0.142 | 69.5 (<0.001) | 0.135 | No |
| Noel SE et al., 2014 (38) |  |  |  |  |  |  |  |  |  |  |  |
| Skin cancer, Basal cell carcinoma | 2 | Cohort | n-3 PUFA intake (high vs. low) | 3840/44539 | RR | 1.05 (0.86, 1.28) | Random | NR | 53.6 (0.14) | NR | No |
| Skin cancer, Squamous cell carcinoma | 2 | CC, Cohort | n-3 PUFA intake (high vs. low) | 1037/2959 | RR | 0.86 (0.59, 1.23) | Random | NR | 52.6 (0.15) | NA | No |
| Skin cancer, Melanoma | 1 | CC | n-3 PUFA intake (high vs. low) | 304/609 | OR | 0.52 (0.34, 0.78) | NA | NR | NA | NA | Yes |

1*n* represents the number of studies included in the meta-analysis.

2Definitions of comparison of each category follow that described in the original studies.

3CC, case control; NA, not assessible; NR, not reported.

**Table 7.** Summary of 12 re-analyses of meta-analyses of fish and omega-3 fatty acid intake and cancer risk with statistically significant results

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of cancer** | **Type of studies** | **Type of omega-3 fatty acid intake1** | **Number of cases** | **Metrices** | **Re-analyzed summary estimate (95% CI)** | ***P*-value** | ***I2*(*P*-value)** | **Egger’s *p*-value** | **Small study effects** | **Prediction interval** | **Excess significance ratio** | **Evidence** | **GRADE certainty** | **Reference** | |
| HCC | CC, Cohort | High total fish intake | 1984 | RR | 0.83 (0.75-0.92) | 3.3E-04 | 0.0 (0.441) | 0.347 | Yes | 0.73-0.95 | 0.75 | Weak | Very low | (36) |
| HCC | Cohort | High total fish intake | 1175 | RR | 0.83 (0.74-0.94) | 0.002 | 0.0 (0.722) | 0.87 | Yes | 0.70-0.99 | 0.77 | Weak | Very low | (36) |
| HCC | Nest CC, Cohort | Fish consumption | NR | RR | 0.72 (0.61-0.86) | 3.05E-04 | 24.117 (0.214) | 0.001 | Yes | 0.50-1.06 | 0.49 | Weak | Very low | (33) |
| HCC | CC, Cohort | n-3 PUFA intake | 583 | RR | 0.49 (0.28-0.85) | 0.011 | 0.0 (0.919) | NA | NA | NA | 1.03 | Weak | Low | (33) |
| Breast cancer | Nest CC, CC, Cohort | Highest marine n-3 PUFA intake | 16178 | RR | 0.86 (0.78-0.94) | 0.002 | 53.796 (0.003) | 0.017 | Yes | 0.63-1.15 | -0.13 | Weak | Very low | (10) |
| Breast cancer | CC, Cohort | Marine n-3 PUFA (Diet) | 11519 | RR | 0.86 (0.76-0.96) | 0.007 | 67.343 (0.001) | 0.028 | Yes | 0.60-1.21 | -0.13 | Weak | Very low | (10) |
| Breast cancer | Cohort | Per 0.1g/day increment of dietary marine n-3 PUFA | 3114 | RR | 0.93 (0.90-0.97) | 3.89E-04 | 0.000 (0.554) | 0.422 | No | 0.73-1.19 | 0.87 | Weak | Moderate | (10) |
| Prostate cancer | Nest CC, CC, Cohort | Per 0.5g/day increase in ALA intakes | 7781 | RR | 0.99 (0.98-1.00) | 0.028 | 0.000 (0.665) | 0.566 | No | 0.98-1.01 | 0.0 | Weak | Low | (32) |
| Prostate cancer | Cohort | ALA intake | NR | RR | 0.91 (0.85-0.98) | 0.017 | 0.000 (0.634) | 0.354 | No | 0.80-1.05 | 0.92 | Weak | Moderate | (31) |
| Prostate cancer | Cohort | Long-chain n-3 | NR | RR | 1.15 (0.99-1.33) | 0.067 | 24.836 (0.249) | NA | NA | NA | 0.63 | Weak | Low | (31) |
| Brain tumor | CC, Cohort | Fish intake (high vs. low) | 4428 | RR | 0.83 (0.70-0.99) | 0.033 | 37.220 (0.121) | 0.024 | Yes | 0.56-1.25 | 0.58 | Weak | Very low | (37) |
| Brain tumor | CC, Cohort | Per 100g/week increase fish intakes | 4428 | RR | 0.95 (0.91-0.98) | 0.007 | 50.736 (0.039) | 0.005 | Yes | 0.86-1.05 | 0.0 | Weak | Very low | (37) |

1Definitions of comparison of each category follow that described in the original studies.

2ALA, alpha-linolenic acid; CC, case control; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NR, not reported.

**Table 8.** Summary of 40 re-analyses of meta-analyses of fish and omega-3 fatty acid intake and cancer risk with not statistically significant results

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of cancer** | **Type of studies** | **Type of omega-3 fatty acid intake1** | **Number of cases** | **Metrices** | **Re-analyzed summary estimate (95% CI)** | ***P*-value** | ***I2*(*P*-value)** | **Egger’s *p*-value** | **Small study effects** | **Prediction interval** | **Excess significance ratio** | **Evidence** | **Reference** |
| Gastric cancer | CC, Cohort | High fish consumption | 5323/136226 | RR | 0.87 (0.71, 1.06) | 0.17 | 73.266 (<0.001) | 0.692 | No | 0.42-1.78 | 1.58 | Non-significant | (41) |
| Colorectal cancer | Cohort | High ω -3 PUFAs intake | 4656/489465 | RR | 0.97 (0.86, 1.10) | 0.66 | 37.546 (0.099) | 0.652 | No | 0.71-1.33 | 1.81 | Non-significant | (39) |
| Colorectal cancer | CC, Cohort | Total n-3 PUFA intake (high vs. low) | 7372/581943 | RR | 0.99 (0.92, 1.06) | 0.76 | 10.492 (0.340) | 0.610 | No | 0.87-1.12 | -3.47 | Non-significant | (30) |
| Colorectal cancer | CC, Cohort | Marine n-3 PUFA intake (high vs. low) | NR | RR | 1.00 (0.93, 1.07) | 0.97 | 0.0 (0.508) | 0.739 | No | 0.92-1.08 | -25.89 | Non-significant | (30) |
| Colorectal cancer | Cohort | Fish consumption (high vs. low) | NR | RR | 0.88 (0.78-1.00) | 0.051 | 14.618 (0.286) | 0.314 | No | 0.35-1.79 | 2.95 | Non-significant | (34) |
| HCC | CC | High total fish intake | 809/10352 | RR | 0.79 (0.59, 1.06) | 0.12 | 41.895 (0.142) | 0.314 | No | 0.35-1.79 | 0.0 | Non-significant | (36) |
| HCC | CC, Cohort | ALA intake | 583/91291 | RR | 0.70 (0.42-1.18) | 0.18 | 0.0 (1.000) | NA | NA | NA | 1.00 | Non-significant | (33) |
| Breast cancer | CC, Cohort | Total n-3 PUFA | NR | RR | 0.96 (0.86, 1.07) | 0.43 | 17.486 (0.282) | 0.068 | Yes | 0.78-1.18 | -0.44 | Non-significant | (10) |
| Breast cancer | Cohort | Per 0.1% energy increment of daily dietary marine n-3 PUFA | 6344/288626 | RR | 0.97 (0.92, 1.02) | 0.22 | 55.285 (0.048) | 0.181 | No | 0.85-1.11 | 0.0 | Non-significant | (10) |
| Breast cancer | CC, Cohort | Highest dietary fish intake | 13323/687770 | RR | 1.03 (0.93, 1.14) | 0.61 | 53.635 (0.009) | 0.596 | No | 0.75-1.40 | 0.0 | Non-significant | (10) |
| Breast cancer | CC, Cohort | Per 15g/day increment of fish intake | 13323/666400 | RR | 1.00 (0.97, 1.03) | 0.98 | 64.5 (<0.001) | 0.847 | No | 0.92-1.09 | -37.77 | Non-significant | (10) |
| Breast cancer | CC, Cohort | Marine n-3 fatty (EPA) | NR | RR | 0.86 (0.75-1.01) | 0.098 | 12.756 (0.174) | 0.051 | Yes | 0.63-1.18 | -0.07 | Non-significant | (10) |
| Breast cancer | CC, Cohort | Marine n-3 fatty (DHA) | NR | RR | 0.89 (0.75, 1.05) | 0.16 | 41.781 (0.079) | 0.164 | No | 0.60-1.32 | -0.17 | Non-significant | (10) |
| Breast cancer | CC, Cohort | Marine n-3 fatty (DPA) | 4746/284724 | RR | 0.91 (0.68, 1.22) | 0.54 | 0.0 (0.933) | 0.800 | No | 0.48-1.72 | 0.68 | Non-significant | (10) |
| Breast cancer | Cohort | ALA(Diet) | 8274/281756 | RR | 0.98 (0.90-1.06) | 0.56 | 5.065 (0.384) | 0.645 | No | 0.85-1.12 | 1.27 | Non-significant | (10) |
| Breast cancer | Cohort | Per 0.1g/day increment of dietary ALA intake | 6310/190451 | RR | 1.00 (0.99-1.01) | 0.54 | 41.644 (0.162) | 0.321 | No | 0.97-1.03 | 0.0 | Non-significant | (10) |
| Breast cancer | Cohort | Per 0.1% energy increment of daily dietary ALA intake | 5510/171680 | RR | 1.00 (0.99, 1.01) | 0.96 | 0.0 (0.771) | 0.440 | No | 0.97-1.04 | 0.0 | Non-significant | (10) |
| Breast cancer | CC, Cohort | ALA (Tissue biomarker and Diet) | 9296/284724 | RR | 0.97 (0.90, 1.04) | 0.39 | 0.0 (0.548) | 0.373 | No | 0.89-1.05 | 0.96 | Non-significant | (10) |
| Endometrial cancer | CC | Dietary omega-3 fatty acids (high vs. low) | 1010/2451 | OR | 0.78 (0.47, 1.30) | 0.35 | 87.184 (0.005) | NA | NA | NA | -0.04 | Non-significant | (35) |
| Endometrial cancer | Cohort | Dietary omega-3 fatty acids (high vs. low) | NR/157456 | HR | 1.03 (0.63, 1.67) | 0.91 | 81.866 (0.004) | 0.590 | No | 0.0-335.28 | -7.58 | Non-significant | (35) |
| Endometrial cancer | Cohort | EPA intake (high vs. low) | NR/157456 | HR | 0.99 (0.61, 1.60) | 0.97 | 82.320 (0.003) | 0.669 | No | 0.0-318.92 | 21.13 | Non-significant | (35) |
| Endometrial cancer | CC | ALA intake (high vs. low) | 1010/2451 | OR | 1.08 (0.84, 1.39) | 0.55 | 28.698 (0.236) | NA | NA | NA | 2.26 | Non-significant | (35) |
| Endometrial cancer | Cohort | ALA intake (high vs. low) | NR/157456 | HR | 0.93 (0.78, 1.09) | 0.37 | 0.0 (0.819) | 0.065 | Yes | 0.31-2.73 | 0.53 | Non-significant | (35) |
| Endometrial cancer | Cohort | DHA intake (high vs. low) | NR/157456 | HR | 1.00 (0.63, 1.59) | 0.99 | 80.457 (0.006) | 0.503 | No | 0.0-237.8 | -111.04 | Non-significant | (35) |
| Endometrial cancer | Cohort | DPA intake (high vs. low) | NR /88774 | HR | 0.86 (0.71, 1.03) | 0.11 | 0.0 (0.888) | NA | NA | NA | 1.04 | Non-significant | (35) |
| Ovarian cancer | CC | Dietary omega-3 fatty acids (high vs. low) | 4269/5803 | OR | 0.79 (0.61, 1.03) | 0.081 | 74.539 (0.020) | 0.766 | No | 0.04-17.31 | 1.00 | Non-significant | (35) |
| Ovarian cancer | CC, Cohort | EPA intake (high vs. low) | 3238/3392 | OR | 0.89 (0.73, 1.08) | 0.25 | 0.0 (0.653) | NA | NA | NA | 1.21 | Non-significant | (35) |
| Ovarian cancer | CC, Cohort | ALA intake (high vs. low) | 4269/5803 | OR | 0.98 (0.77, 1.26) | 0.90 | 58.606 (0.089) | 0.943 | No | 0.07-13.89 | -11.17 | Non-significant | (35) |
| Ovarian cancer | CC, Cohort | DHA intake (high vs. low) | 3238/3392 | OR | 0.91 (0.75, 1.11) | 0.34 | 0.0 (0.789) | NA | NA | NA | 0.86 | Non-significant | (35) |
| Prostate cancer | Cohort | Per 0.05g/day increase in EPA intake | 7778/450999 | RR | 1.02 (0.99, 1.05) | 0.25 | 30.635 (0.217) | 0.709 | No | 0.94-1.10 | 1.10 | Non-significant | (32) |
| Prostate cancer | CC | High fish consumption | 5777/9805 | OR | 0.86 (0.72, 1.02) | 0.074 | 47.291 (0.035) | 0.507 | No | 0.53-1.37 | 1.43 | Non-significant | (40) |
| Prostate cancer | Cohort | High fish consumption | 13924/445820 | RR | 1.05 (0.91, 1.21) | 0.51 | 61.981 (0.002) | 0.671 | No | 0.70-1.58 | 0.83 | Non-significant | (40) |
| Prostate cancer | Cohort | Total omega 3 intake | NR /93047 | RR | 1.15 (0.99, 1.33) | 0.067 | 24.836 (0.249) | NA | NA | NA | 0.63 | Non-significant | (31) |
| Prostate cancer | Cohort | EPA intake | NR /151326 | RR | 1.08 (0.92, 1.25) | 0.34 | 42.662 (0.175) | 0.658 | No | 0.24-4.88 | 0.13 | Non-significant | (31) |
| Prostate cancer | Cohort | DHA intake | NR /196192 | RR | 1.08 (0.91, 1.27) | 0.40 | 51.445 (0.128) | 0.539 | No | 0.19-6.25 | -0.14 | Non-significant | (31) |
| Prostate cancer | Cohort | Long-chain n-3 +(DHA+EPA) | NR /82483 | RR | 1.03 (0.97, 1.10) | 0.28 | 0.0 (0.461) | 0.339 | No | 0.95-1.13 | -0.30 | Non-significant | (31) |
| Lung cancer | Cohort | PUFA intake (high vs low) | NR/1268442 | RR | 0.91 (0.78, 1.06) | 0.23 | 67.739 (0.001) | 0.186 | No | 0.58-1.44 | -0.11 | Non-significant | (42) |
| Lung cancer | Cohort | PUFA intake (per 5g/day increment) | NR/1268442 | RR | 0.98 (0.96, 1.01) | 0.14 | 69.484 (<0.001) | 0.135 | No | 0.93-1.04 | 0.0 | Non-significant | (42) |
| Skin cancer, Basal cell carcinoma | Cohort | n-3 PUFA intake (high vs. low) | 3840/44539 | RR | 1.05 (0.86, 1.28) | 0.64 | 53.633 (0.142) | NA | Na | NA | 2.53 | Non-significant | (38) |
| Skin cancer, Squamous cell carcinoma | CC, Cohort | n-3 PUFA intake (high vs. low) | 1037/2959 | RR | 0.85 (0.60, 1.21) | 0.38 | 49.990 (0.157) | NA | NA | NA | -0.12 | Non-significant | (38) |

1Definitions of comparison of each category follow that described in the original studies.

2ALA, alpha-linolenic acid; CC, case control; DPA, docosapentaenoic acid; NA, not assessible.

**Table 9.** Sensitivity analysis of meta-analyses of fish and omega-3 fatty acid intake and cancer risk by study design (Cohort and case-control)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & year, type of cancer** | **Type of omega-3 fatty acid intake1** | **Observational studies** | | | **Cohort** | | | **Case-control** | | |
|  |  | *n*2 | Summary estimate (95% CI)3 | Level of evidence | *n*2 | Summary estimate (95% CI)3 | Level of evidence | *n*2 | Summary estimate (95% CI)3 | Level of evidence |
| Wu S et al., 2011 (41) |  |  |  |  |  |  |  |  |  |  |
| Gastric cancer | High fish consumption | 17 | 0.87 (0.71, 1.07) | Not significant | 2 | 1.10 (0.75, 1.61) | Not significant | 15 | 0.85 (0.68, 1.06) | Not significant |
| Chen G-C et al., 2015 (30) |  |  |  |  |  |  |  |  |  |  |
| Colorectal cancer | Total n-3 PUFA intake (high vs. low) | 10 | 0.99 (0.92-1.06) | Not significant | 2 | 1.02 (0.92, 1.12) | Not significant | 11 | 0.97 (0.87, 1.08) | Not significant |
| Colorectal cancer | Marine n-3 PUFA intake (high vs. low) | 11 | 1.00 (0.93-1.07) | Not significant | 2 | 1.04 (0.92, 1.17) | Not significant | 9 | 0.98 (0.90, 1.07) | Not significant |
| Zheng J-S et al., 2013 (10) |  |  |  |  |  |  |  |  |  |  |
| Breast cancer | Highest marine n-3 PUFA intake | 17 | 0.86 (0.78-0.94) | Weak | 11 | 0.86 (0.77, 0.96) | Weak | 6 | 0.83 (0.67, 1.03) | Not significant |
| Breast cancer | Total n-3 PUFA | 10 | 0.96 (0.86-1.06) | Not significant | 4 | 0.99 (0.91, 1.08) | Not significant | 6 | 0.95 (0.61, 1.19) | Not significant |
| Breast cancer | Highest dietary fish intake | 11 | 1.03 (0.93-1.14) | Not significant | 9 | 1.05 (0.94, 1.18) | Not significant | 2 | 0.83 (0.57, 1.20) | Not significant |
| Breast cancer | Per 15g/day increment of fish intake | 11 | 1.00 (0.97-1.03) | Not significant | 9 | 1.00 (0.97, 1.03) | Not significant | 2 | 0.92 (0.72, 1.19) | Not significant |
| Breast cancer | Marine n-3 fatty (EPA) | 10 | 0.93 (0.85-1.02) | Not significant | 4 | 0.89 (0.74, 1.07) | Not significant | 6 | 0.78 (0.60, 1.02) | Not significant |
| Breast cancer | Marine n-3 fatty (DHA) | 10 | 0.88 (0.75-1.03) | Not significant | 4 | 0.92 (0.74, 1.15) | Not significant | 6 | 0.83 (0.63, 1.08) | Not significant |
| Breast cancer | Marine n-3 fatty (DPA) | 4 | 0.99 (0.98, 1.01) | Not significant | 1 | 0.94 (0.63, 1.38) | Not significant | 3 | 0.89 (0.56, 1.42) | Not significant |
| Breast cancer | ALA (Tissue biomarker and Diet) | 12 | 0.97 (0.90, 1.04) | Not significant | 6 | 0.97 (0.90, 1.06) | Not significant | 6 | 0.87 (0.67, 1.12) | Not significant |
| Hoang T et al., 2018 (35) |  |  |  |  |  |  |  |  |  |  |
| Ovarian cancer | ALA intake (high vs. low) | 3 | 0.99 (0.77, 1.26) | Not significant | 1 | 1.00 (0.72, 1.39) | Not significant | 2 | 0.97 (0.66, 1.43) | Not significant |
| Lian W et al., 2017 (37) |  |  |  |  |  |  |  |  |  |  |
| Brain tumor | Fish intake (high vs. low) | 9 | 0.83 (0.70, 0.99) | Weak | 1 | 1.05 (0.82, 1.34) | Not significant | 8 | 0.79 (0.66, 0.95) | Weak |
| Brain tumor | Per 100g/week increase fish intakes | 9 | 0.95 (0.91, 0.98) | Weak | 1 | 0.96 (0.92, 1.01) | Not significant | 8 | 0.94 (0.89, 0.99) | Weak |
| Noel SE et al., 2014 (38) |  |  |  |  |  |  |  |  |  |  |
| Skin cancer, Squamous cell carcinoma | n-3 PUFA intake (high vs. low) | 3 | 0.86 (0.59, 1.23) | Not significant | 2 | 0.98 (0.71, 1.36) | Not significant | 1 | 0.70 (0.49, 1.00) | Not significant |

1Definitions of comparison of each category follow that described in the original studies.

2*n* represents the number of studies included in the meta-analysis.

3All summary estimate and 95% CI were obtained by re-analysis. They were based on random-effects model.

4ALA, alpha-linolenic acid; DPA, docosapentaenoic acid; NA, not assessible.

**Figure legends**

Figure 1. Flow chart of the literature search