REVIEW

Consumption of Fish and ω-3 Fatty Acids and Cancer Risk: An Umbrella Review of Meta-Analyses of Observational Studies

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ABSTRACT

Multiple studies have suggested that ω-3 fatty acid intake may have a protective effect on cancer risk; however, its true association with cancer risk remains controversial. We performed an umbrella review of meta-analyses to summarize and evaluate the evidence for the association between ω-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 intake of fish or ω-3 fatty acid and cancer risk (gastrointestinal, liver, breast, gynecologic, prostate, brain, lung, and skin) and determined the level of evidence of associations. In addition, we appraised the quality of the evidence of significant meta-analyses by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) 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 ω-3 fatty acid intake and

risk of the following types of cancer: 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). In the other 3 meta-analyses, studies of endometrial cancer and skin cancer, there were no assessable data for determining the evidence levels. No meta-analysis showed convincing, highly suggestive, or suggestive evidence of an association. In the sensitivity analysis of meta-analyses by study design, we found weak associations between ω-3 fatty acid intake and breast cancer risk in cohort studies, but no statistically significant association in case-control studies. However, the opposite results were found in case of brain tumor risk. Although ω-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 nonsignificant or weak evidence level, clinicians and researchers should cautiously interpret reported associations between ω-3 fatty acid consumption and cancer risks. *Adv Nutr* 2020;00:1–16.

Keywords: ω-3 fatty acid, fish, cancer, umbrella review, meta-analysis

Introduction

ω-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 one of the important resources for the human body. ω-3 Fatty acids include long-chain α-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, because EPA and DHA are generated from ALA in the body, their dietary consumption is not considered essential for human health (3). ω-3 Fatty acids can be ingested from ALA-containing plant oil, which can be obtained from walnuts, flaxseed, and canola (4). EPA and DHA can be supplemented by eating fatty fish such as albacore tuna, salmon, mackerel, sardines, and herring (5). ω-3 Fatty acids are incorporated into 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, which are assumed to be effective in preventing or treating several diseases (8).

Multiple animal studies and in vitro studies have supported the association of the consumption of fish high in ω-3 fatty acids with reduced cancer risk. ω-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). Later epidemiological studies and meta-analyses also examined the putative effects of ω-3 fatty acid supplementation on various cancers (10, 11). However, these reviews have generated conflicting results and did not include comprehensive appraisals and consideration of biases and uncertainty in the body of evidence used to support claims of causal associations.

Recently, a new approach called the 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 has not always had positive effects on clinical decisions (15). Recently published meta-analyses, including those in nutrition, only give a limited perspective of results by examining the effect of a specific intervention on a specific outcome. In studies of different types of cancer included in previously published meta-analyses, differences in types and doses of ω-3 fatty acids have affected the conclusions obtained and led to contradictory and inconsistent meta-analysis findings. A systematic approach to providing evidence is thus needed.

Given the aforementioned shortcomings of previous data, we set out to provide an overview and evaluate the validity of reported associations of ω-3 fatty acids with various cancer risks by perform 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 ω-3 fatty acids and cancer risk.

Methods

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

Search strategy of the literature

We performed an umbrella review of the systematic reviews and meta-analyses on associations between ω-3 fatty acid intake and cancer risks. Three investigators (JIS, HJS, and EKC) performed a search of PubMed, Embase, and the Cochrane Database of Systematic Reviews, restricted to articles published in English. The search included studies publisehd through December 1, 2018, without any limitation of the publication date. We used the following search terms: (ω-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

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Supplemental Table 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances.
Abbreviation used: ALA, α-linolenic acid; AMSTAR2, A Measurement Tool to Assess Systematic Reviews 2; CUP, Continuous Update Project; DPA, docosapentaenoic acid; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCC, hepatocellular carcinoma; 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.

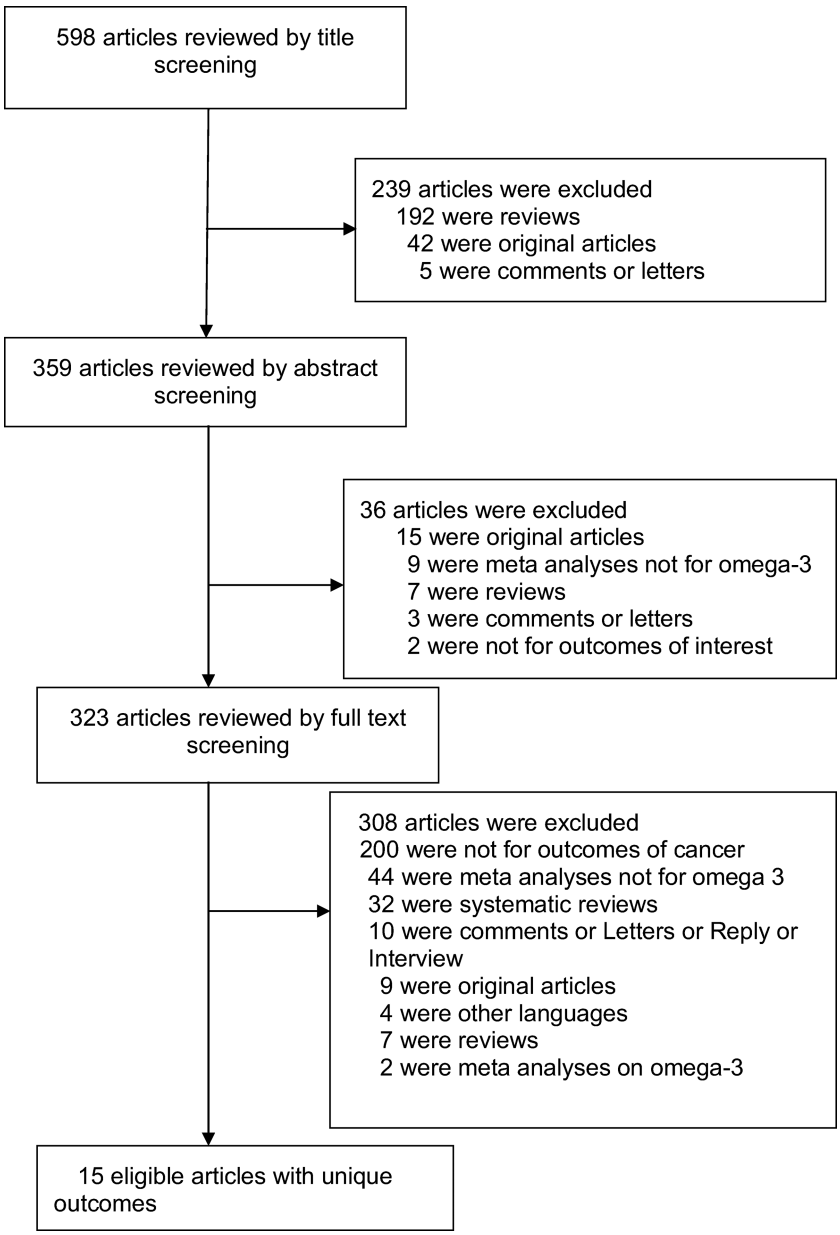

FIGURE 1 Flow chart of the literature search.

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 reviews and meta-analyses that examined the association between ω-3 fatty acid and cancer risk. We excluded studies that *1*) examined genetic polymorphisms related to ω-3 fatty acid metabolism; *2*) had ω-3 fatty acid status as the outcome; *3*) dealt with cost-effectiveness of ω-3 fatty acid supplementation; *4*) were meta-analyses in which the treatment arm contained several compounds, including ω-3 fatty acids; *5*) were meta-analyses focusing on the ratio of ω-3/ω-6 PUFA; *6*) did 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 was evaluated using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR2) (17). This instrument is a 16-point assessment tool for evaluating methodological aspects of included studies and provides a rationale for item selection and identifies critical domains for assessment of the validity of the results of systematic reviews and meta-analyses. Study validity is classified as high,

TABLE 1 Summary of the meta-analyses of fish and ω-3 fatty acid intake and gastrointestinal cancer risk[1]

Author & year, type of cancer	*n*	Type of studies	Type of ω-3 fatty acid intake[2]	Cases/total participants	Type of metrics	Summary effect size (95% CI)	Model	*P* value	I^2 (*P* value)	Egger's *P* value	Statistically significant
Wu S et al., 2011 (18)											
Gastric cancer	17	CC, cohort	High fish consumption	5323/136,226	RR	0.87 (0.71, 1.07)	Random	NR	73.3 (<0.001)	0.59	No
Shen X-J et al., 2012 (19)											
Colorectal cancer	7	Cohort	High ω-3 PUFAs intake	4656/489,465	RR	0.97 (0.86, 1.10)	Random	NR	38.1 (0.08)	NR	No
Chen G-C et al., 2015 (20)											
Colorectal cancer	10	CC, cohort	Total n-3 PUFA intake (high vs. low)	7372/581,943	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 (21)											
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. CC, case control; NR, not reported.
[2] Definitions of comparison of each category follow that described in the original studies.

TABLE 2 Summary of the meta-analyses of fish and ω-3 fatty acid intake and liver cancer risk[1]

Author & year, type of cancer	*n*	Type of studies	Type of ω-3 fatty acid intake[2]	Cases/total participants	Type of metrics	Summary effect size (95% CI)	Model	*P* value	I^2 (*P*)	Egger's *P* value	Statistically significant
Huang R-X et al., 2015 (22)											
HCC	10	CC, cohort	High total fish intake	1984/5,370,040	RR	0.82 (0.71, 0.94)	Random	0.018	12.8 (0.325)	0.07	Yes
HCC	5	CC	High total fish intake	809/10,352	RR	0.79 (0.59, 1.06)	Random	0.27	41.9 (0.142)	NR	No
HCC	5	Cohort	High total fish intake	1175/5,359,688	RR	0.82 (0.70, 0.96)	Random	0.011	0.0 (0.487)	NR	Yes
Gao M et al., 2015 (23)											
HCC	11	CC, cohort	Fish consumption	NR/1,196,005	RR	0.65 (0.51, 0.79)	Random	NR	44.1 (0.057)	<0.01	Yes
HCC	2	CC, cohort	n-3 PUFA intake	583/91,291	RR	0.49 (0.19, 0.79)	Random	NR	0.0 (0.929)	NA	Yes
HCC	2	CC, cohort	ALA intake	583/91,291	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. ALA, alpha-linolenic acid; CC, case control; HCC, hepatocellular carcinoma; NR, not reported.
[2] Definitions of comparison of each category follow that described in the original studies.

moderate, low, or critically low instead of using an overall score. The detailed results obtained with these rating criteria are shown in **Supplemental Table 1**.

Extraction of the data

Data were extracted by 3 investigators (GK, HP, and EJ), and any discrepancies were discussed and resolved by consensus. For each eligible review, we gathered the outcome data of the meta-analyses. We also abstracted the names of the first author and the journal, publication year, type of outcome, types of patients, study design (cohort and/or case-control), number of studies, type of metric (RR, OR, or HR, as reported by the authors of the meta-analysis), effect sizes with corresponding 95% CIs, meta-analysis model (fixed/random), the P value for overall effects, I^2 or chi-squared value 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 reanalyzed the eligible meta-analyses extracted from the previously published studies. We collected all of the included individual studies and performed reanalysis using Comprehensive Meta-Analysis software version 3.3.070 (Biostat). Then, we summarized different summary effect sizes with corresponding 95% 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 associations (24–26).

We assessed the heterogeneity between studies using I^2, which ranges from 0 to 100%, and the P value of the chi-square–based Cochran Q test (27). I^2 is the ratio of between-study variance to the sum of the within- and between-study variances (28). I^2 values >50 % or >75 % are usually interpreted as having large or very large heterogeneity, respectively (28). We also evaluated small-study effects, commonly known as publication bias, to identify whether such studies tend to give much larger risk estimates than large studies (29). By using the regression asymmetry test proposed by Egger and colleagues, we assessed small-study effects indicating publication and other reporting bias (30). An Egger P value <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 number of statistically significant studies in a meta-analysis with the observed number (31). 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 <1 indicating the presence of excess significance bias (32). For statistically significant meta-analyses, we also appraised the quality of the evidence from each meta-analysis by using the GRADE system (33).

Level of evidence of associations

Based on results of our reanalysis of the eligible meta-analysis, we further grouped the associations between ω-3 fatty acids and cancer risks according to the criteria from conventional umbrella reviews (15, 34) with the following components: evidence of strong statistical significance using random-effects meta-analyses at $P < 10^{-6}$, magnitude of between-study heterogeneity $I^2 < 50\%$, number of cases with binary outcomes >1000, absence of small study effects (Egger $P \geq 0.10$), and 95% PI that excluded the null.

Convincing evidence required strong statistical significance in a meta-analysis, with $P < 10^{-6}$, the absence of large heterogeneity ($I^2 < 50\%$), number of cases with binary outcomes >1000, no evidence of small-study effects (Egger P value > 0.10) and excess significance bias, and 95% PI excluding the null.

Highly suggestive evidence required strong statistical significance, with $P < 10^{-6}$, 95% PI including the null, number of cases >1000, and the presence of large heterogeneity ($I^2 > 50\%$), small-study effects, and excess significance bias.

Suggestive evidence required a significant association, with $P < 0.001$, 95% PI including the null, number of cases >1000, the presence of large heterogeneity ($I^2 > 50\%$), small-study effects, and excess significance bias.

Weak evidence was that for which there was large heterogeneity ($I^2 > 50\%$) or publication bias and evidence of small-study effects. Even if there was not large heterogeneity ($I^2 \leq 50\%$) or publication bias or excess significance bias, a small number of cases (<1000) or a nominally significant association ($P = 0.001$–0.05) would be observed.

Nonsignificant associations had $P > 0.05$.

If a meta-analysis included only 1 study, the between-study heterogeneity and Egger P value were not available. In this case, we determined the level was not assessable (NA).

Reanalysis of meta-analyses by study design

We further processed the sensitivity analysis by study design. Using 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 a reanalysis. Meta-analyses including only 1 cohort and case-control study, respectively, were not accounted for in the sensitivity analysis. We then evaluated the level of evidence of the outcome from reanalysis.

Results

Overall summary of meta-analyses

A total of 598 articles were initially identified, with exclusions of duplicated articles, and 15 eligible articles with 57 meta-analyses were included in our review. We systematically categorized 57 meta-analyses into 6 cancer-risk categories as follows: gastrointestinal cancer, liver cancer, breast cancer, gynecologic cancer, prostate cancer, and

TABLE 3 Summary of the meta-analyses of fish and ω-3 fatty acid intake and breast cancer risk[1]

Author & year, type of cancer	*n*	Type of studies	Type of ω-3 fatty acid intake[2]	Cases/total participants	Type of metrics	Summary effect size (95% CI)	Model	*P* value	I^2 (*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	16,178/527,392	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)	11,519/443,619	RR	0.85 (0.76, 0.96)	Random	NR	67 (0.001)	NR	Yes
Breast cancer	3	Cohort	Per 0.1g/d increment of dietary marine n-3 PUFA	3114/117,488	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	6344/288,626	RR	0.95 (0.90, 1.00)	Random	NR	79 (<0.001)	NR	No
Breast cancer	11	CC, cohort	Highest dietary fish intake	13,323/687,770	RR	1.03 (0.93, 1.14)	Random	NR	54 (0.009)	0.6	No
Breast cancer	11	CC, cohort	Per 15 g/d increment of fish intake	13,323/666,400	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)	4746/284,724	RR	0.90 (0.69, 1.19)	Random	NR	0.0 (NR)	NR	No
Breast cancer	6	Cohort	ALA(Diet)	8274/281,756	RR	0.98 (0.90, 1.06)	Random	NR	5.1 (0.384)	NR	No
Breast cancer	4	Cohort	Per 0.1 g/d increment of dietary ALA intake	6310/190,451	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	5510/171,680	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)	9296/284,724	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. ALA, α-linolenic acid; CC, case-control; DPA, docosapentaenoic acid; NR, not reported.
[2] Definitions of comparison of each category follow those described in the original studies.

brain/lung/skin cancer (10, 18–23, 35–42). Brain/lung/skin cancer was assessed in groups due to small numbers of meta-analyses.

Gastrointestinal cancer outcomes

Among 5 meta-analyses identified from the literature search, all showed no association of cancer risk with ω-3 fatty acid intake. The studies were on gastric cancer ($n = 1$) and colorectal cancer ($n = 4$) (**Table 1**).

Liver cancer outcomes

Six meta-analyses of the association of ω-3 fatty acids and liver cancer were identified. Among these, 4 meta-analyses were statistically significant, with reduction of cancer incidence with ω-3 fatty acid intake. The other 2 meta-analyses revealed no associations (**Table 2**).

Breast cancer outcomes

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

Gynecologic cancer outcomes

Among 14 meta-analyses, 2 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 1 case-control study. The other meta-analyses did not affect the incidence of ovarian cancer ($n = 7$) or endometrial cancer ($n = 5$) (**Table 4**).

Prostate cancer outcomes

Among 11 meta-analyses, 3 meta-analyses showed statistically significant results for the association between ω-3 fatty acid intake and prostate cancer ($n = 3$). Of 3 results, 1 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 2 meta-analyses found a protective effect of ω-3 intake. One study showed a marginally nonsignificant 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, 3 reported statistically significant associations. Two studies revealed a significant reduced incidence of brain tumors with ω-3 fatty acid intake ($n = 2$ of 2). Also, a meta-analysis consisting of 1 case-control study found a significantly reduced risk of melanoma. Contrary to the results above, there was no association between the ω-3 fatty acid intake and lung ($n = 2$) or 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 endometrial cancer were not assessable because they contained only 1 individual study. Of the remaining 12 associations, no study showed convincing or suggestive evidence of association. All meta-analyses with statistically significant findings showed weak evidence, as follows: 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 results, but the level of evidence was not applicable due to lack of included studies. The other 42 meta-analyses were nonsignificant.

Among 12 meta-analyses with weak levels of evidence, 5 (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, 7 studies (58.3%) showed evidence of small-study effects (Egger P value < 0.10). In case of GRADE assessment, 2 meta-analyses on breast and prostate cancer were rated as moderate certainty and 3 on hepatocellular carcinoma (HCC) and prostate cancer showed low certainty. The other 7 meta-analyses were rated as very low certainty.

Out of 42 nonsignificant associations, 40 meta-analyses showed a nonsignificant levels of evidence ($P > 0.05$). One outcome of meta-analysis was unavailable for reanalysis due to insufficient information on individual studies used for meta-analysis. The other study only included a single individual study, so the level of evidence was not assessible (**Table 8**).

Reanalysis of meta-analyses by study design

Among 57 meta-analyses analyzed in our study, 15 of them included both case-control and cohort studies in a single meta-analysis (**Table 9**). For investigations of 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. Although 2 studies of brain tumors showed weak levels of evidence on meta-analyses of both observational studies and case-control studies, these findings were not significant in cohort studies. However, the pooled meta-analysis of observational studies included only 1 case-control study, and thus this meta-analysis should be interpreted cautiously.

Discussion

Our umbrella review is to our knowledge the first reported study to examine the evidence from meta-analyses of observational studies on the relation between ω-3 fatty acid intake and cancer risk. Extensive data were provided by 15 eligible articles, with a total of 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

TABLE 4 Summary of the meta-analyses of ω-3 fatty acid intake and gynecologic cancer risk[1]

Author & year, type of cancer	*n*	Type of studies	Type of ω-3 fatty acid intake[2]	Cases/total participants	Type of metrics	Summary effect size (95% CI)	Model	*P* value	I^2 (*P* value)	Egger's *P* value	Statistically significant
Hoang T et al., 2019 (38)											
Endometrial cancer	2	CC	Dietary ω-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 ω-3 fatty acids (high vs. low)	NR/157,456	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/157,456	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/157,456	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/157,456	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/88,774	HR	0.86 (0.71, 1.03)	Random	NR	0.0 (NR)	NA	No
Ovarian cancer	3	CC	Dietary ω-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. ALA, α-linolenic acid; CC, case control; DPA, docosapentaenoic acid; NA, not assessible; NR, not reported.
[2] Definitions of comparison of each category follow that described in the original studies.

TABLE 5 Summary of the meta-analyses of fish and ω-3 fatty acid intake and prostate cancer risk[1]

Author & year, type of cancer	*n*	Type of studies	Type of ω-3 fatty acid intake[2]	Cases/total participants	Type of metrics	Summary effect size (95% CI)	Model	*P* value	I^2 (*P* value)	Egger's *P* value	Statistically significant
Fu Y-Q et al., 2015 (37)											
Prostate cancer	5	Cohort	Per 0.5 g/d increase in ALA intake	7781/430,090	RR	0.99 (0.98, 1.00)	Random	NR	0.0 (0.670)	NR	Yes
Prostate cancer	5	Cohort	Per 0.05 g/d increase in EPA intake	7778/450,999	RR	1.02 (0.99, 1.05)	Random	NR	36.1 (0.181)	NR	No
Szymanski KM et al., 2010 (41)											
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	13,924/445,820	RR	1.01 (0.90, 1.14)	Random	0.83	59 (0.005)	0.84	No
Alexander DD et al., 2015 (35)											
Prostate cancer	13	Cohort	High ω-3 PUFA intake (diet)	NR/446,243	SRRE	1.00 (0.93, 1.09)	Random	NR	50.4 (0.019)	NR	No
Chua ME et al., 2012 (36)											
Prostate cancer	4	Cohort	ALA intake	NR/177,133	RR	0.92 (0.85, 0.99)	Random	0.019	0 (0.677)	0.34	Yes
Prostate cancer	2	Cohort	Total ω 3 intake	NR/93,047	RR	0.97 (0.89, 1.07)	Random	0.549	20 (0.264)	NR	No
Prostate cancer	3	Cohort	EPA intake	NR/151,326	RR	1.05 (0.96, 1.15)	Random	0.317	41 (0.182)	0.65	No
Prostate cancer	3	Cohort	DHA intake	NR/196,192	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/30,731	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/82,483	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. ALA, α-linolenic acid; CC, case control; NA, not assessible; NR, not reported.
[2] Definitions of comparison of each category follow that described in the original studies.

TABLE 6 Summary of the meta-analyses of fish and ω-3 fatty acid intake and brain, lung, and skin cancer risk[1]

Author & year, type of cancer	*n*	Type of studies	Type of ω-3 fatty acid intake[2]	Cases/total participants	Type of metrics	Summary effect size (95% CI)	Model	*P* value	I^2 (*P* value)	Egger's *P* value	Statistically significant
Lian W et al., 2017 (39)											
Brain tumor	9	CC, cohort	Fish intake (high vs. low)	4428/505,296	RR	0.83 (0.70, 0.99)	Random	NR	37.5 (0.119)	0.02	Yes
Brain tumor	9	CC, cohort	Per 100 g/wk increase fish intakes	4428/505,296	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/1,268,442	RR	0.91(0.78, 1.06)	Random	0.230	67.7 (0.001)	0.186	No
Lung cancer	11	Cohort	PUFA intake (per 5 g/d increment)	NR/1,268,442	RR	0.98 (0.96, 1.01)	Random	0.142	69.5 (<0.001)	0.135	No
Noel SE et al., 2014 (40)											
Skin cancer, basal cell carcinoma	2	Cohort	n-3 PUFA intake (high vs. low)	3840/44,539	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. CC, case control; NA, not assessible; NR, not reported.
[2] Definitions of comparison of each category follow that described in the original studies.

TABLE 7 Summary of 12 reanalyses of meta-analyses of fish and ω-3 fatty acid intake and cancer risk with statistically significant results[1]

Type of cancer	Type of studies	Type of ω-3 fatty acid intake	Number of cases	Metrices	Reanalyzed summary estimate (95% CI)	*P* value	I^2 (*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	(22)
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	(22)
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	(23)
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	(23)
Breast cancer	Nest CC, CC, cohort	Highest marine n-3 PUFA intake	16,178	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)	11,519	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 0.1 g/d 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 0.5 g/d 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	(37)
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	(36)
Prostate cancer	Cohort	Long-chain n-3	NR	RR	1.14 (1.01, 1.28)	0.036	24.836 (0.249)	NA	NA	NA	0.63	Weak	Low	(36)
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	(39)
Brain tumor	CC, cohort	Per 100 g/wk 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	(39)

[1] Definitions of comparison of each category follow that described in the original studies. ALA, alpha-linolenic acid; CC, case control; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NR, not reported.

TABLE 8 Summary of 40 reanalyses of meta-analyses of fish and ω-3 fatty acid intake and cancer risk with no statistically significant results[1]

Type of cancer	Type of studies	Type of ω-3 fatty acid intake	Number of cases	Metrices	Reanalyzed summary estimate (95% CI)	*P* value	I^2 (*P* value)	Egger's *P* value	Small-study effects	Prediction interval	Excess significance ratio	Evidence	Reference
Gastric cancer	CC, cohort	High fish consumption	5323/136,226	RR	0.87 (0.71, 1.06)	0.17	73.266 (<0.001)	0.692	No	0.42–1.78	1.58	Nonsignificant	(18)
Colorectal cancer	Cohort	High ω-3 PUFAs intake	4656/489,465	RR	0.97 (0.86, 1.10)	0.66	37.546 (0.099)	0.652	No	0.71–1.33	1.81	Nonsignificant	(19)
Colorectal cancer	CC, cohort	Total n-3 PUFA intake (high vs. low)	7372/581,943	RR	0.99 (0.92, 1.06)	0.76	10.492 (0.340)	0.610	No	0.87–1.12	− 3.47	Nonsignificant	(20)
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	Nonsignificant	(20)
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	Nonsignificant	(21)
HCC	CC	High total fish intake	809/10,352	RR	0.79 (0.59, 1.06)	0.12	41.895 (0.142)	0.314	No	0.35–1.79	0.0	Nonsignificant	(22)
HCC	CC, cohort	ALA intake	583/91,291	RR	0.70 (0.42–1.18)	0.18	0.0 (1.000)	NA	NA	NA	1.00	Nonsignificant	(23)
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	Nonsignificant	(10)
Breast cancer	Cohort	Per 0.1% energy increment of daily dietary marine n-3 PUFA	6344/288,626	RR	0.97 (0.92, 1.02)	0.22	55.285 (0.048)	0.181	No	0.85–1.11	0.0	Nonsignificant	(10)
Breast cancer	CC, cohort	Highest dietary fish intake	13,323/687,770	RR	1.03 (0.93, 1.14)	0.61	53.635 (0.009)	0.596	No	0.75–1.40	0.0	Nonsignificant	(10)
Breast cancer	CC, cohort	Per 15 g/d increment of fish intake	13,323/666,400	RR	1.00 (0.97, 1.03)	0.98	64.5 (<0.001)	0.847	No	0.92–1.09	− 37.77	Nonsignificant	(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	Nonsignificant	(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	Nonsignificant	(10)
Breast cancer	CC, cohort	Marine n-3 fatty (DPA)	4746/284,724	RR	0.91 (0.68, 1.22)	0.54	0.0 (0.933)	0.800	No	0.48–1.72	0.68	Nonsignificant	(10)
Breast cancer	Cohort	ALA (diet)	8274/281,756	RR	0.98 (0.90–1.06)	0.56	5.065 (0.384)	0.645	No	0.85–1.12	1.27	Nonsignificant	(10)
Breast cancer	Cohort	Per 0.1 g/d increment of dietary ALA intake	6310/190,451	RR	1.00 (0.99–1.01)	0.54	41.644 (0.162)	0.321	No	0.97–1.03	0.0	Nonsignificant	(10)
Breast cancer	Cohort	Per 0.1% energy increment of daily dietary ALA intake	5510/171,680	RR	1.00 (0.99, 1.01)	0.96	0.0 (0.771)	0.440	No	0.97–1.04	0.0	Nonsignificant	(10)
Breast cancer	CC, cohort	ALA (tissue biomarker and diet)	9296/284,724	RR	0.97 (0.90, 1.04)	0.39	0.0 (0.548)	0.373	No	0.89–1.05	0.96	Nonsignificant	(10)
Endometrial cancer	CC	Dietary ω-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	Nonsignificant	(38)
Endometrial cancer	Cohort	Dietary ω-3 fatty acids (high vs. low)	NR/157,456	HR	1.03 (0.63, 1.67)	0.91	81.866 (0.004)	0.590	No	0.0–335.28	− 7.58	Nonsignificant	(38)
Endometrial cancer	Cohort	EPA intake (high vs. low)	NR/157,456	HR	0.99 (0.61, 1.60)	0.97	82.320 (0.003)	0.669	No	0.0–318.92	21.13	Nonsignificant	(38)
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	Nonsignificant	(38)
Endometrial cancer	Cohort	ALA intake (high vs. low)	NR/157,456	HR	0.93 (0.78, 1.09)	0.37	0.0 (0.819)	0.065	Yes	0.31–2.73	0.53	Nonsignificant	(38)

(*Continued*)

TABLE 8 (*Continued*)

Type of cancer	Type of studies	Type of ω-3 fatty acid intake	Number of cases	Metrices	Reanalyzed summary estimate (95% CI)	*P* value	I^2 (*P* value)	Egger's *P* value	Small-study effects	Prediction interval	Excess significance ratio	Evidence	Reference
Endometrial cancer	Cohort	DHA intake (high vs. low)	NR/157,456	HR	1.00 (0.63, 1.59)	0.99	80.457 (0.006)	0.503	No	0.0–237.8	− 111.04	Nonsignificant	(38)
Endometrial cancer	Cohort	DPA intake (high vs. low)	NR/88,774	HR	0.86 (0.71, 1.03)	0.11	0.0 (0.888)	NA	NA	NA	1.04	Nonsignificant	(38)
Ovarian cancer	CC	Dietary ω-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	Nonsignificant	(38)
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	Nonsignificant	(38)
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	Nonsignificant	(38)
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	Nonsignificant	(38)
Prostate cancer	Cohort	Per 0.05 g/d increase in EPA intake	7778/450,999	RR	1.02 (0.99, 1.05)	0.25	30.635 (0.217)	0.709	No	0.94–1.10	1.10	Nonsignificant	(37)
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	Nonsignificant	(41)
Prostate cancer	Cohort	High fish consumption	13,924/445,820	RR	1.05 (0.91, 1.21)	0.51	61.981 (0.002)	0.671	No	0.70–1.58	0.83	Nonsignificant	(41)
Prostate cancer	Cohort	Total ω 3 intake	NR/93,047	RR	1.15 (0.99, 1.33)	0.067	24.836 (0.249)	NA	NA	NA	0.63	Nonsignificant	(36)
Prostate cancer	Cohort	EPA intake	NR/151,326	RR	1.08 (0.92, 1.25)	0.34	42.662 (0.175)	0.658	No	0.24–4.88	0.13	Nonsignificant	(36)
Prostate cancer	Cohort	DHA intake	NR/196,192	RR	1.08 (0.91, 1.27)	0.40	51.445 (0.128)	0.539	No	0.19–6.25	− 0.14	Nonsignificant	(36)
Prostate cancer	Cohort	Long-chain n-3 +(DHA + EPA)	NR/82,483	RR	1.03 (0.97, 1.10)	0.28	0.0 (0.461)	0.339	No	0.95–1.13	− 0.30	Nonsignificant	(36)
Lung cancer	Cohort	PUFA intake (high vs low)	NR/1,268,442	RR	0.91 (0.78, 1.06)	0.23	67.739 (0.001)	0.186	No	0.58–1.44	− 0.11	Nonsignificant	(42)
Lung cancer	Cohort	PUFA intake (per 5 g/d increment)	NR/1,268,442	RR	0.98 (0.96, 1.01)	0.14	69.484 (<0.001)	0.135	No	0.93–1.04	0.0	Nonsignificant	(42)
Skin cancer, Basal cell carcinoma	Cohort	n-3 PUFA intake (high vs. low)	3840/44,539	RR	1.05 (0.86, 1.28)	0.64	53.633 (0.142)	NA	NA	NA	2.53	Nonsignificant	(40)
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	Nonsignificant	(40)

[1] Definitions of comparison of each category follow that described in the original studies.
[2] ALA, α-linolenic acid; CC, case control; DPA, docosapentaenoic acid; NA, not assessible.

TABLE 9 Sensitivity analysis of meta-analyses of fish and ω-3 fatty acid intake and cancer risk by study design (cohort and case-control)[1]

Author & year, type of cancer	Type of ω-3 fatty acid intake[2]	Observational studies			Cohort			Case-control		
		n	Summary estimate (95% CI)[3]	Level of evidence	*n*	Summary estimate (95% CI)[3]	Level of evidence	*n*	Summary estimate (95% CI)[3]	Level of evidence
Wu S et al., 2011 (18)										
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 (20)										
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 15 g/d 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., 2019 (38)										
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 (39)										
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 100 g/wk 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 (40)										
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

[1] *n* represents the number of studies included in the meta-analysis. ALA, α-linolenic acid; DPA, docosapentaenoic acid; NA, not assessible.
[2] Definitions of comparison of each category follow that described in the original studies.
[3] All summary estimates and 95% CIs were obtained by reanalysis. They were based on a random-effects model.

of significance, using collected data (e.g., *P* for overall effect, *P* for heterogeneity, and I^2 and *P* for publication bias, prediction intervals, and numbers of participants). All 12 meta-analyses for the effects of ω-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 weak evidence. Three meta-analyses of studies of endometrial cancer and skin cancer also showed significant results, but only contained a single individual study, and the level of evidence was not assessable.

In 1 study there was a positive association between long-chain n-3 intake and risk of prostate cancer. However, this study only included 2 individual cohorts, with a *P* value showing a nominal significance (P = 0.036), which should be interpreted cautiously.

In the present study, we not only focused on a specific type of ω-3 fatty acids but also included the various types of ω-3 fatty acids. Conventional meta-analyses only focus on a single comparison with a single outcome, which is a design through which it is difficult to broadly understand a subject. To overcome this limitation, the goal of our umbrella review is to help clinicians and researchers develop an extensive understanding of the current evidence for the association of ω-3 fatty acid intake with cancer, and therefore we included studies of different sources of ω-3 fatty acid in the current investigation. Regarding the sources of ω-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%).

As shown in Table 9, we found that high intake of marine n-3 PUFA significantly reduced the risk of breast cancer in meta-analyses of both observational and cohort studies; however, findings were not significant in analyses of reported case-control studies (10). Despite the nonsignificant result from the meta-analysis of case-control studies, the direction of the outcomes was consistent between case-control and cohort studies. This result is attributable to the design of the included 11 cohort studies, which investigated effects prospectively, a approach that is considered to be more reliable than other methods. In contrast, in studies of of brain tumor, high consumption of fish showed a positive effect in the meta-analyses of both case-control and observational studies; however, the analyses also showed a negative effect for the cohort study design. Given these points, it is important to consider meta-analyses of both case-control and cohort studies when drawing conclusions.

Our results revealed that few studies on ω-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, investigators should also consider the effect size, 95% CI, heterogeneity, publication bias, and funnel plot data (28, 29, 43). Using a method that follows the conventional criteria makes it possible to establish the level of evidence much more 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). In single meta-analyses, statistical methods are frequently inadequate and misused (45), which can result in misleading outcomes, distortion, and bias. Recently, the practice of establishing 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 investigated in the current study primarily presented their results with random- or fixed-effects sizes and 95% CIs with *P* values. However, to determine the noteworthiness of the results, it was important to conduct further analysis of between-study heterogeneity and small-study effects (30, 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 4 statistically significant results. This limitation explains the need to comprehensively interpret the meta-analyses using an umbrella review.

The public considers ω-3 fatty acids to be beneficial for health, a viewpoint that has led to the consumption of fish oil supplements. Reflecting this trend, much research has assessed the potential association of ω-3 fatty acids with health outcomes, with a special focus on disease reduction, an approach that has led to conflicting results. Nevertheless, no comprehensive study on ω-3 fatty acids has specifically studied levels of evidence. Moreover, most recent evidence from a randomized controlled trial highlighted findings indicating that supplementation with ω-3 fatty acids did not significantly lower the incidence of cancer, which supports our finding (11).

In addition, we compared our final results with those of the report from the Word Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR). According to the latest report published from the 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, in studies of other cancers, including head and neck, lung, stomach, pancreas, gallbladder, ovary, endometrium, prostate, kidney, bladder, and skin cancer, the authors draw conclusions with "limited–no conclusion" evidence. In our study, the results of 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, ω-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 available studies, suggesting that further studies are needed to confirm these findings. The lack of

strong evidence regarding HCC may also be partly explained by the multifactorial etiology of such tumor types. Indeed, relevant biological differences in responses to ω-3 fatty acid may exist in cases of viruses-related neoplasms compared with HCC associated with a particular environmental risk factor compared with others.

The mechanisms of the cancer preventive effect of ω-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 ω-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 ω-3 fatty acids on overall organ-specific cancer risk is the combining of 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 predefined systematic search strategy. Second, we did not reanalyze all the data. Third, an original observational study could be cited in 2 or more meta-analyses. Even though 1 meta-analysis that has better quality should be selected for 1 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 degrees or definitions of high or low intakes may cross 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 ω-3 intake on cancer risks. Further meta-research articles on levels or ratios of ω-3 fatty acid components or cancer mortality need to be explored in future studies.

Conclusion

In conclusion, although ω-3 fatty acids are commonly used as dietary supplements and many studies on ω-3 fatty acids have been published, there was no convincing evidence related to the effects of ω-3 fatty acids on cancer risk. Weak evidence supported the association between ω-3 fatty acids and breast cancer, HCC, prostate cancer, and brain tumor. From the results separating the study design, we found that there was a discrepancy in the association of ω-3 fatty acids with breast cancer and brain tumor. To draw a consistent outcome with a high level of evidence, further studies are needed to identify the actual effects of ω-3 fatty acids on cancer risks by using 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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