Review

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

Keum Hwa Lee [1,†], Hyo Jin Seong [2,†], Gaeun Kim [3,†], Gwang Hun Jeong [4,†], Hyunbong Park [5], Eunyoung Jung [5], Andreas Kronbichler [6], Michael Eisenhut [7], Jong Yeob Kim [2], Brendon Stubbs [8,9,10], Marco Solmi [11], Ai Koyanagi [12,13], Sung Hwi Hong [2,14], Elena Dragioti [15], Leandro Fórnias Machado de Rezende [16], Louis Jacob [12,17], NaNa Keum [18,19], Hans J. van der Vliet [30], Eunyoung Cho [21,22], Nicola Veronese [23], Giuseppe Grosso [24], Shuji Ogino [25,26,27,28], Mingyang Song [18,26,29,30], Joaquim Radua [31,32,33,34], Sun Jae Jung [26,35], Trevor Thompson [36,], Sarah E. Jackson [37], Lee Smith [38], Lin Yang [39,40], Eun Kyoung Choi [41,*], Jae Il Shin [1,**], Hans Oh [42], Edward L. Giovannucci [18,22,] and Gabriele Gamerith [43]

1. Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
2. Yonsei University College of Medicine, Seoul, Republic of Korea
3. Keimyung University College of Nursing, Daegu, Republic of Korea
4. College of Medicine, Gyeongsang National University, Jinju, Republic of Korea
5. Yonsei University Graduate School, Department of Nursing, Seoul, Republic of Korea
6. Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria;
7. Department of Pediatrics, Luton & Dunstable University Hospital NHS Foundation Trust, , Luton, United Kingdom
8. Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

9. South London and Maudsley NHS Foundation Trust, London, United Kingdom
10. Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, United Kingdom
11. Department of Neuroscience, University of Padova, Padova, Italy
12. Parc Sanitari Sant Joan de Déu/CIBERSAM, Universitat de Barcelona, Fundació Sant Joan de Déu,Sant Boi de Llobregat, Barcelona, Spain
13. ICREA, Pg. Lluis Companys 23, Barcelona, Spain
14. Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA, USA
15. Pain and Rehabilitation Centre, and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden
16. Universidade Federal de São Paulo. Escola Paulista de Medicina. Departamento de Medicina Preventiva. São Paulo - SP, Brasil.
17. Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France
18. Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA, USA
19. Department of Food Science and Biotechnology, Donggguk University, Goyang, Republic of Korea
20. Department of Medical Oncology, Amsterdam UMC, Cancer Center Amsterdam, VU University, Amsterdam, The Netherlands
21. Department of Dermatology, The Warren Alpert Medical School, Brown University, Providence, RI, USA
22. Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
23. National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy

24. Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy
25. Cancer Immunology and Cancer Epidemiology Programs, Dana-Farber Harvard Cancer Center, Boston, MA, USA
26. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA;
27. Program in MPE Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
28. Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge, MA, USA
29. Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
30. Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
31. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
32. Mental Health Research Networking Center (CIBERSAM), Barcelona, Spain
33. Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
34. Centre for Psychiatric Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
35. Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
36. Department of Psychology, University of Greenwich, London, United Kingdom
37. Department of Behavioral Science and Health, University College London, London, United Kingdom

38. The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Chelmsford, United Kingdom
39. Department of Cancer Epidemiology and Cancer Prevention, Alberta Health Services, Calgary, Canada
40. Departments of Oncology and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Canada
41. Mo-Im Kim Nursing Research Institute, Yonsei University College of Nursing, Seoul, Republic of Korea
42. School of Social Work, University of Southern California, CA, USA
43. Department of Medical Oncology, Medical University Innsbruck, Innsbruck, Austria

†These authors contributed equally to this work.

****** Correspondence: Jae Il Shin, M.D., Ph.D.

Address: Yonsei-ro 50, Seodaemun-gu, C.P.O. Box 8044, Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Republic of Korea.

Tel.: +82-2-2228-2050; Fax: +82-2-393-9118; E-mail: shinji@yuhs.ac

*****Co-Correspondence: Eun Kyoung Choi, Ph.D.

Address: Yonsei-ro 50, Seodaemun-gu, Mo-Im Kim Nursing Research Institute, Yonsei University College of Nursing, Seoul 03722, Republic of Korea

Tel.: +82-2-2228-3340; Fax: +82-2-2227-9303; E-mail: ekchoi@yuhs.ac

Sources of Support: We did not receive any funding for this study.

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

Abstract

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

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

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

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

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

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

Introduction

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

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

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

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

Materials and Methods

Search strategy of the literatures

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

Eligibility and inclusion/exclusion criteria

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

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

Extraction of the data

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

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

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

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

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

Level of evidence of associations

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

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

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

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

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

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

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

Results

Overall summary of meta-analyses

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

Gastrointestinal cancer outcomes

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

Hepatobiliary cancer outcomes

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

Breast cancer outcomes

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

Gynecologic cancer outcomes

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

Prostate cancer outcomes

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

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

Brain/lung/skin cancer outcomes

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

Levels of evidence of association

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

Acknowledgments

Author Contributions: Conceptualization, S.H.J. and J.I.S.; methodology, J.I.S.; validation, E.K.C., S.H.J., K.H.L., H.P., G.K., and J.I.S.; formal analysis, K.H.L., H.P., G.K. and G.H.J.; data curation, E.K.C., S.H.J. and J.I.S.; writing—original draft preparation, K.H.L., E.K.C., M.E., A.K., and J.I.S.,; writing—review and editing, K.H.L., H.J.S., G.K., G.H.J., H.P., E.J., A.K., M.E., J.Y.K., B.S., M.S., A.K., S.H.H., E.D., L.F.M.R., L.J., N.K., H.J.v.d.V., E.C., N.V., E.L.G., G.G., S.O., M.S., J.R., S.J.J., T.T., S.E.J., L.S., L.Y., H.O., E.K.C., J.I.S. and G.G.

Funding: We did not receive either financial support or grants associated with the topics discussed in this manuscript. Brendon Stubbs is supported by a Clinical Lectureship (ICA-CL-2017-03-001) jointly funded by Health Education England (HEE) and the National Institute for Health Research (NIHR). Brendon Stubbs is part funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust. Brendon Stubbs is also supported by the Maudsley Charity, King's College London and the NIHR South London Collaboration for Leadership in Applied Health Research and Care (CLAHRC) funding. This paper presents independent research. The views expressed in this publication are those of the authors and not necessarily those of the acknowledged institutions.

Conflicts of Interest: The authors disclose no conflicts of interest.

References

1. Bradberry JC, Hilleman DE. Overview of omega-3 Fatty Acid therapies. P T 2013;38(11):681-91.
2. Nettleton JA. Omega-3 fatty acids: comparison of plant and seafood sources in human nutrition. J Am Diet Assoc 1991;91(3):331-7.
3. Tur JA, Bibiloni MM, Sureda A, *et al.* Dietary sources of omega 3 fatty acids: public health risks and benefits. Br J Nutr 2012;107 Suppl 2:S23-52.
4. Kris-Etherton PM, Harris WS, Appel LJ, *et al.* Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. Arterioscler Thromb Vasc Biol 2003;23(2):151-2.
5. Surette ME. The science behind dietary omega-3 fatty acids. CMAJ 2008;178(2):177-80.
6. Lazzarin N, Vaquero E, Exacoustos C, *et al.* Low-dose aspirin and omega-3 fatty acids improve uterine artery blood flow velocity in women with recurrent miscarriage due to impaired uterine perfusion. Fertil Steril 2009;92(1):296-300.
7. Krauss-Etschmann S, Shadid R, Campoy C, *et al.* Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: a European randomized multicenter trial. Am J Clin Nutr 2007;85(5):1392-400.
8. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 2008;8(5):349-61.
9. Zheng JS, Hu XJ, Zhao YM, *et al.* Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ 2013;346:f3706.
10. Manson JE, Cook NR, Lee IM, *et al.* Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med 2019;380(1):23-32.
11. Poole R, Kennedy OJ, Roderick P, *et al.* Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ 2017;359:j5024.
12. Khan SU, Khan MU, Riaz H, *et al.* Effects of Nutritional Supplements and Dietary Interventions on Cardiovascular Outcomes: An Umbrella Review and Evidence Map. Ann Intern Med 2019; 10.7326/M19-0341.
13. Tsilidis KK, Kasimis JC, Lopez DS, *et al.* Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015;350:g7607.
14. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009;172(1):137-159.
15. Graham PL, Moran JL. Robust meta-analytic conclusions mandate the provision of prediction intervals in meta-analysis summaries. J Clin Epidemiol 2012;65(5):503-10.
16. Higgins JP. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. Int J Epidemiol 2008;37(5):1158-60.
17. Belbasis L, Bellou V, Evangelou E, *et al.* Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. Lancet Neurol 2015;14(3):263-73.
18. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. BMJ 2007;335(7626):914-6.
19. Sterne JA, Sutton AJ, Ioannidis JP, *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj 2011;343:d4002.
20. Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315(7109):629-34.

21. Choi EK, Park HB, Lee KH, *et al.* Body mass index and 20 specific cancers: re-analyses of dose-response meta-analyses of observational studies. Ann Oncol 2018;29(3):749-757.
22. Cappelleri JC, Ioannidis JP, Schmid CH, *et al.* Large trials vs meta-analysis of smaller trials: how do their results compare? JAMA 1996;276(16):1332-8.
23. Ioannidis JP, Tarone R, McLaughlin JK. The false-positive to false-negative ratio in epidemiologic studies. Epidemiology 2011;22(4):450-6.
24. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? BMJ 2001;322(7280):226-31.
25. Alexander DD, Bassett JK, Weed DL, *et al.* Meta-Analysis of Long-Chain Omega-3 Polyunsaturated Fatty Acids (LComega-3PUFA) and Prostate Cancer. Nutr Cancer 2015;67(4):543-54.
26. Chen GC, Qin LQ, Lu DB, *et al.* N-3 polyunsaturated fatty acids intake and risk of colorectal cancer: meta-analysis of prospective studies. Cancer Causes Control 2015;26(1):133-41.
27. Chua ME, Sio MC, Sorongon MC, *et al.* Relationship of dietary intake of omega-3 and omega-6 Fatty acids with risk of prostate cancer development: a meta-analysis of prospective studies and review of literature. Prostate Cancer 2012;2012:826254.
28. Fu YQ, Zheng JS, Yang B, *et al.* Effect of individual omega-3 fatty acids on the risk of prostate cancer: a systematic review and dose-response meta-analysis of prospective cohort studies. J Epidemiol 2015;25(4):261-74.
29. Gao M, Sun K, Guo M, *et al.* Fish consumption and n-3 polyunsaturated fatty acids, and risk of hepatocellular carcinoma: systematic review and meta-analysis. Cancer Causes Control 2015;26(3):367-76.
30. Geelen A, Schouten JM, Kamphuis C, *et al.* Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. Am J Epidemiol 2007;166(10):1116-25.
31. Hoang T, Myung SK, Pham TT. Dietary Intake of Omega-3 fatty acids and Endocrine-related Gynecological Cancer: A Meta-Analysis of Observational Studies. Cancer Res Treat 2019;51(3):1022-1032.
32. Huang RX, Duan YY, Hu JA. Fish intake and risk of liver cancer: a meta-analysis. PLoS One 2015;10(1):e0096102.
33. Lian W, Wang R, Xing B, *et al.* Fish intake and the risk of brain tumor: a meta-analysis with systematic review. Nutr J 2017;16(1):1.
34. Noel SE, Stoneham AC, Olsen CM, *et al.* Consumption of omega-3 fatty acids and the risk of skin cancers: a systematic review and meta-analysis. Int J Cancer 2014;135(1):149-56.
35. Shen XJ, Zhou JD, Dong JY, *et al.* Dietary intake of n-3 fatty acids and colorectal cancer risk: a meta-analysis of data from 489 000 individuals. Br J Nutr 2012;108(9):1550-6.
36. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr 2010;92(5):1223-33.
37. Wu S, Liang J, Zhang L, *et al.* Fish consumption and the risk of gastric cancer: systematic review and meta-analysis. BMC Cancer 2011;11:26.
38. Zhang YF, Lu J, Yu FF, *et al.* Polyunsaturated fatty acid intake and risk of lung cancer: a meta-analysis of prospective studies. PLoS One 2014;9(6):e99637.
39. Lau J, Ioannidis JP, Terrin N, *et al.* The case of the misleading funnel plot. BMJ 2006;333(7568):597-600.
40. Aromataris E, Fernandez R, Godfrey CM, *et al.* Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc 2015;13(3):132-40.

41. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. Cmaj 2009;181(8):488-93.
42. Herrmann D, Sinnett P, Holmes J, *et al.* Statistical controversies in clinical research: publication bias evaluations are not routinely conducted in clinical oncology systematic reviews. Ann Oncol 2017;28(5):931-937.
43. WCRF/AICR. Continuous Update Project Report. Meat, Fish and Dairy Products and the Risk of Cancer. World Cancer Research Fund/American Institute for Cancer Research: Washington, DC, USA 2018.
44. Cockbain AJ, Toogood GJ, Hull MA. Omega-3 polyunsaturated fatty acids for the treatment and prevention of colorectal cancer. Gut 2012;61(1):135-49.
45. Larsson SC, Kumlin M, Ingelman-Sundberg M, *et al.* Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 2004;79(6):935-45.
46. Song M, Nishihara R, Cao Y, *et al.* Marine omega-3 Polyunsaturated Fatty Acid Intake and Risk of Colorectal Cancer Characterized by Tumor-Infiltrating T Cells. JAMA Oncol 2016;2(9):1197-206.
47. Ogino S, Chan AT, Fuchs CS, *et al.* Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. Gut 2011;60(3):397-411.
48. Ogino S, Nishihara R, VanderWeele TJ, *et al.* Review Article: The Role of Molecular Pathological Epidemiology in the Study of Neoplastic and Non-neoplastic Diseases in the Era of Precision Medicine. Epidemiology 2016;27(4):602-11.

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

Author(year) Outcome	No. of studies	Type of studies	Type of omega-3 intake	Cases/total participants	Type of metrics	Summary effect size (95% CI)	Model	P-value	I^2 (P-value)	Egger (P-value)	Statistically significance
Wu (2011)											
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 (2012)											
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 (2015)											
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 (2007)											
Colorectal cancer	14	Cohort	Fish consumption (high vs. low)	NR	RR	0.88 (0.78, 1.00)	Random	NR	18.3 (0.25)	0.66	No

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

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

Author(year) **Outcome**	**No. of studies**	**Type of studies**	**Type of omega-3 intake**	**Cases/total participants**	**Type of metrics**	**Summary effect size (95% CI)**	**Model**	**P-value**	**I^2 (P-value)**	**Egger** (P-value)	**Statistically significance**
Huang (2015)											
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 (2015)											
HCC	11	Nest CC, Cohort	Fish consumption	NR/1196005	RR	0.65 (0.51, 0.79)	Random	NR	44.1 (0.057)	<0.01	Yes
HCC	2	Cohort, CC	n-3 PUFA intake	583/91291	RR	0.49 (0.19, 0.79)	Random	NR	0.0 (0.929)	NA	Yes
HCC	2	Cohort, CC	ALA intake	583/91291	RR	0.70 (0.30, 1.10)	Random	NR	0.0 (1.000)	NA	No

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

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

Author(year) **Outcome**	**No. of studies**	**Type of studies**	**Type of omega-3 intake**	**Cases/total participants**	**Type of metrics**	**Summary effect size (95% CI)**	**Model**	**P-value**	**I^2 (P-value)**	**Egger** (P-value)	**Statistically significance**
Zheng (2013)											
Breast cancer	19	Nest CC, 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	Nest CC, Cohort	Total n-3 PUFA	NR	RR	0.96 (0.86, 1.06)	Random	NR	13 (NR)	0.04	No
Breast cancer	11	CC, 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	6	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	14	Nest CC, 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	14	Nest 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	11	Nest CC, CC, Cohort	Marine n-3 fatty (EPA)	NR	RR	0.93 (0.85, 1.02)	Random	NR	2.9 (NR)	NR	No
Breast cancer	11	Nest CC, CC, Cohort	Marine n-3 fatty (DHA)	NR	RR	0.88 (0.75, 1.03)	Random	NR	37.6 (NR)	NR	No
Breast cancer	5	Nest CC, 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	CC, Cohort	ALA(Diet)	8274/281756	RR	0.98 (0.90, 1.06)	Random	NR	5.1 (0.384)	NR	No
Breast cancer	4	CC, 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	Nest CC, 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

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

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

Author(year) **Outcome**	**No. of studies**	**Type of studies**	**Type of omega-3 intake**	**Cases/total participants**	**Type of metrics**	**Summary effect size (95% CI)**	**Model**	**P-value**	**I^2 (P-value)**	**Egger** (P-value)	**Statistically significance**
Hoang (2018)											
Endometrial cancer	5	CC, Cohort	Dietary omega-3 fatty acids (high vs. low)	NR/159907	OR/HR	0.95 (0.72, 1.26)	Random	NR	67.3 (NR)	NR	No
Endometrial cancer	4	CC, Cohort	EPA intake (high vs. low)	NR /158999	OR/HR	0.86 (0.58, 1.30)	Random	NR	81.3 (NR)	NR	No
Endometrial cancer	5	CC, Cohort	ALA intake (high vs. low)	NR /159907	OR/HR	0.93 (0.81, 1.08)	Random	NR	0.0 (NR)	NR	No
Endometrial cancer	4	CC, Cohort	DHA intake (high vs. low)	NR /158999	OR/HR	0.89 (0.63, 1.28)	Random	NR	76.1 (NR)	NR	No
Endometrial cancer	2	CC, Cohort	DPA intake (high vs. low)	NR /88774	OR/HR	0.86 (0.71, 1.03)	Random	NR	0.0 (NR)	NA	No
Ovarian cancer	3	CC	Dietary omega-3 fatty acids (high vs. low)	4269/5803	OR	0.79 (0.61-1.03)	Random	NR	74.5 (NR)	NR	No
Ovarian cancer	2	CC	EPA intake (high vs. low)	3238/3392	OR	0.89 (0.73, 1.08)	Random	NR	71.5 (NR)	NA	No
Ovarian cancer	3	CC	ALA intake (high vs. low)	4269/5803	OR	0.99 (0.77, 1.26)	Random	NR	58.6 (NR)	NR	No
Ovarian cancer	2	CC	DHA intake (high vs. low)	3238/3392	OR	0.91 (0.75, 1.11)	Random	NR	0.0 (NR)	NA	No
Ovarian cancer	1	CC	DPA intake (high vs. low)	1366/1414	OR	1.06 (0.85, 1.33)	NA	NR	NA	NA	No

Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; OR, odds ratio; HR, hazard ratio; NR, not reported; CC, case-control; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acids; DPA, docosapentaenoic acid; NA, not assessible

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

Author(year) **Outcome**	**No. of studies**	**Type of studies**	**Type of omega-3 intake**	**Cases/total participants**	**Type of metrics**	**Summary effect size (95% CI)**	**Model**	**P-value**	**I^2 (P-value)**	**Egger** (P-value)	**Statistically significance**
Fu (2015)											
Prostate cancer	5	Nest CC, CC, Cohort	Per 0.5g/day increase in ALA intake	7781/430090	RR	0.99 (0.98, 1.00)	Random	-NR	0.0 (0.670)	NR	Yes
Prostate cancer	5	Nest CC, CC, Cohort	Per 0.05g/day increase in EPA intake	7778/450999	RR	1.02 (0.99, 1.05)	Random	NR	36.1 (0.181)	NR	No
Szymanski (2010)											
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 (2015)											
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 (2012)											
Prostate cancer	4	Cohort	ALA intake	NR/177133	RR	0.92 (0.85, 0.99)	Random	0.019	0 (0.677)	0.34	Yes
Prostate cancer	2	Cohort	Total omega 3 intake	NR /93047	RR	0.97 (0.89, 1.07)	Random	0.549	20 (0.264)	NR	No
Prostate cancer	3	Cohort	EPA intake	NR /151326	RR	1.05 (0.96, 1.15)	Random	0.317	41 (0.182)	0.65	No
Prostate cancer	3	Cohort	DHA intake	NR /196192	RR	1.03 (0.94, 1.13)	Random	0.489	52 (0.127)	0.54	No
Prostate cancer	2	Cohort	Long-chain n-3	NR /30731	RR	1.14 (1.01, 1.28)	Random	0.036	25 (0.249)	NA	Yes
Prostate cancer	4	Cohort	Long-chain n-3 +(DHA+EPA)	NR /82483	RR	1.03 (0.97, 1.10)	Random	0.278	0 (0.462)	0.51	No

Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; CC, case-control; OR, odds ratio; RR, risk ratio; SRRE, summary relative risk estimates; NR, not reported; NA, not assessible; ω, omega; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acids; PUFAs, polyunsaturated fatty acids

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

Author(year) **Outcome**	**No. of studies**	**Type of studies**	**Type of omega-3 intake**	**Cases/total participants**	**Type of metrics**	**Summary effect size (95% CI)**	**Model**	**P-value**	**I^2 (P-value)**	**Egger** (P-value)	**Statistically significance**
Lian (2017)											
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 (2014)											
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 (2014)											
Skin cancer, Basal cell carcinoma	3	Cohort	n-3 PUFA intake (high vs. low)	NR/44539	RR	1.05 (0.86, 1.28)	Random	NR	53.6 (0.14)	NR	No
Skin cancer, Squamous cell carcinoma	2	CC, Cohort	n-3 PUFA intake (high vs. low)	NR/1890	RR	0.86 (0.59, 1.23)	Random	NR	52.6 (0.15)	NA	No
Skin cancer, Melanoma	1	CC	n-3 PUFA intake (high vs. low)	304/609	OR	0.52 (0.34, 0.78)	NA	NR	NA	NA	Yes

Abbreviations: No., number; Random effects, summary effect size (95% CI) using random effects model; CC, case-control; OR, odds ratio; RR, risk ratio; NR, not reported; NA, not assessible; PUFA, polyunsaturated fatty acid

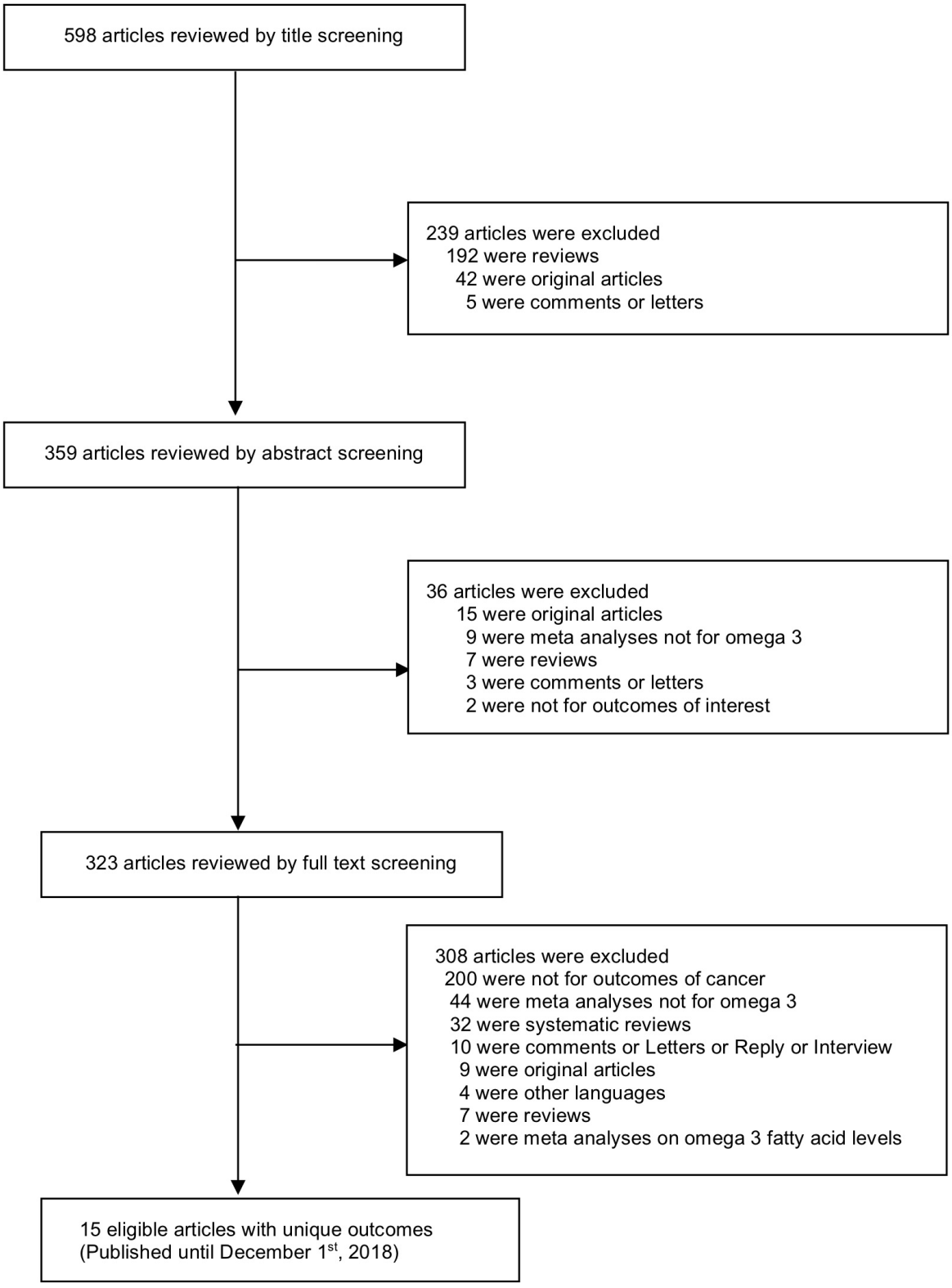
Table 7. Summary of 12 re-analyses of meta-analyses with statistically significant results

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

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

Figure legends

Figure 1. Flow chart of the literature search


598 articles reviewed by title screening
239 articles were excluded
192 were reviews
42 were original articles
5 were comments or letters
359 articles reviewed by abstract screening
36 articles were excluded
15 were original articles
9 were meta analyses not for omega 3
7 were reviews
3 were comments or letters
2 were not for outcomes of interest
323 articles reviewed by full text screening
308 articles were excluded
200 were not for outcomes of cancer
44 were meta analyses not for omega 3
32 were systematic reviews
10 were comments or Letters or Reply or Interview
9 were original articles
4 were other languages
7 were reviews
2 were meta analyses on omega 3 fatty acid levels
15 eligible articles with unique outcomes
(Published until December 1st, 2018)