Original Article

Gynecological cancer and omega-3 fatty acid intakes: Meta-analysis

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Background and Objectives: Previous observational epidemiological studies have reported inconsistent findings on the association between dietary intake of omega-3 fatty acids and endocrine-related gynecological cancer including ovarian cancer and endometrial cancer. This study aimed to investigate this association using a meta-analysis of observational studies. **Methods and Study Design:** We searched PubMed, EMBASE, and Cochrane library by using keywords related to the topic in December 2019. The pooled odd ratios (pORs), pooled relative risks (pRRs), or pooled hazard ratios (pHRs) with 95% confidence intervals (CIs) were calculated based on a random-effects model. Also, we performed subgroup analyses by methodological quality, type of cancer, study design, and type of omega-3 fatty acids. **Results:** A total of 10 observational studies with six case-control and four prospective cohort studies were included in the current meta-analysis. In the meta-analysis of all studies, dietary intake of omega-3 fatty acids was not significantly associated with the risk of endometrial and ovarian cancers (pOR/HR, 0.87; 95% CI, 0.73-1.04; I^2=67.2%) (highest versus lowest intake). In the subgroup analysis by type of study, no significant association was found in cohort studies (pHR, 1.03; 95% CI, 0.63-1.67, I^2=81.9%), whereas dietary intake of omega-3 fatty acids was associated with the decreased risk of endocrine-related gynecological cancers in case-control studies (pOR, 0.81; 95% CI, 0.67 to 0.98, I^2=55.7%). **Conclusions:** The current meta-analysis of observational studies suggests that dietary intake of omega-3 fatty acids is not significantly associated with the risk of endocrine-related gynecological cancer.

Key Words: Omega-3 fatty acids, endometrial cancer, ovarian cancer, observational study, meta-analysis

INTRODUCTION

Endometrial cancer and ovarian cancer, which are called endocrine-related gynecological cancers, are the most common and second common type of gynecological malignancies, respectively.[1] There are several risk factors for endometrial cancer, which include body mass index (BMI), parity, age at menarche, oral contraceptives, diabetes, and smoking.[2] Getting older is associated with an increased risk of ovarian cancer, while factors that interrupt ovulation such as use of oral contraceptives, pregnancy or breastfeeding are known to be associated with the decreased risk of ovarian cancer.[2]

Previous observational studies have reported that there was a significant association between biomarkers of inflammation such as C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-alpha and the risk of endometrial cancer[3-5] and ovarian cancer.[6] Meta-analyses of observational studies have also suggested that non-steroidal anti-inflammatory drugs might have a protective effect against these cancers.[3,7,8] Moreover, both non-interventional studies[9,10] and randomized clinical trials[11-13] reported that omega-3 fatty acids such as alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA) have potential anti-inflammatory effects.[3] Regarding the potential effects of omega-3 fatty acids on the risk of endocrine-related gynecological cancers, several observational studies such as case-control studies and cohort

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studies[3,14-22] have reported inconsistent findings. However, no meta-analysis has been published on this topic.

The current study aimed to investigate the associations between dietary intake of omega-3 fatty acids and endocrine-related gynecological cancers by using a meta-analysis of observational epidemiological studies such as case-control studies and cohort studies and subgroup meta-analyses by various factors such as type of cancer, type of study design, type of omega-3 fatty acids, and study quality.

METHODS

Literature search

Three different databases including MEDLINE (PubMed), EMBASE, and the Cochrane Library were systematically searched from their inception to December 2019 by using common keywords related to omega-3 fatty acids and endocrine-related gynecological cancers. The keywords for literature search were as follows: ("omega-3 fatty acid" OR "fish oil" OR "eicosapentaenoic acid" OR "alpha-linolenic acid" OR "docosahexaenoic acid" OR "docosapentaenoic acid") AND ("endometrial cancer" OR "uterine cancer" OR "ovarian cancer"). The bibliographies of relevant studies were also reviewed to identify additional publications. The languages of publication were not limited.

Study selection and eligibility criteria

The following are eligibility criteria for individual studies included in the meta-analysis: observational epidemiological studies such as case-control studies and prospective or retrospective cohort studies; studies that investigated the associations between dietary intake of omega-3 fatty acids and the risk of endocrine-related gynecological cancer. For studies having the same study population, the higher quality study or the first published one was included in the final analysis. Based on the eligibility criteria, two investigators (TH and TTP) independently selected the potential studies.

Methodological quality assessment

We assessed methodological qualities of the included studies based on the Newcastle Ottawa Scale for observational studies.[23] The Newcastle Ottawa Scale consists of 3 subscales such as the selection of studies, comparability, and exposure. Its star system ranges between 0 and 9. In our study, a study given more than a mean score in each study type was considered as having high quality.

Main and subgroup analyses

In the main analysis, we investigated the association between dietary intake of overall omega-3 fatty acids (highest versus lowest intake) and the risk of endocrine-related gynecological cancer. Subgroup meta-analyses were performed by type of study (case-control study or cohort study), type of cancer (endometrial cancer or ovarian cancer), type of omega-3 fatty acids (ALA, EPA, DHA, or DPA), and methodological quality of study (high vs low).

Among the included 10 studies, two studies (Bidoli et al[15] and Tavani et al[16]) were from the same study population. To avoid overlaps, we included Tavani et al in the main analysis and Bidoli et al's study in the subgroup analysis according to type of cancer.

Statistical analyses

We used adjusted ORs, RRs, or HRs with 95% CIs from individual studies to calculate a pooled effect size. To measure heterogeneity across studies, we used Higgins I^2,[24] which is calculated as the following formula:

$I^2 = 100\% \times (Q - df) / Q$,

where Q is Cochran's heterogeneity statistic and df is the degrees of freedom. Negative values of I^2 are set at zero; I^2 ranges from 0% (no heterogeneity) to 100% (maximal heterogeneity). If I^2 value is greater than 50%, it represents substantial heterogeneity.[25] Because individual studies were conducted in different populations, the random-effects model with the DerSimonian and Laird method was used to calculate the pooled effect size.[26]

Publication bias was assessed by using the Begg's funnel plot and Egger's test.[27,28] If the funnel plot is asymmetric or the *p*-value for Egger's test is lower than 0.05, there exists publication bias. The Stata SE version 14.0 software (StataCorp, College Station, Texas, USA) was used for all statistical analyses.

RESULTS

Selection of relevant studies

Supplementary figure 1 illustrates a flow diagram to identify relevant studies. A total of 4,730 articles were obtained from three databases. Among them, 375 duplicate articles were excluded. After reviewing the title and abstract of each article, we excluded 4,311 articles that did not satisfy the selection criteria. Among them, 34 articles were excluded after reviewing the full texts of the remaining 44 articles. The reasons for exclusion were not relevant to the study topic (n=9) and insufficient data for study outcome (n=25). A total of ten studies with six case-control studies[15-18,20,22] and four cohort studies[3,14,19,21] were included in the final analysis.

General characteristics of studies

The general characteristics of the nine studies included in the final analysis are summarized in Table 1. The included studies were five case-control studies with a total of 12,523 participants consisting of 5,279 cases and 7,244 controls, which were published between 2002 and 2014, and four cohort studies with a total of 237,714 participants, which were published between 2002 and 2016. They were conducted in the United States (n=6), Italy (n=2), and Australia (n=1). The follow-up periods ranged between 1980 and 2013.

Methodological quality of studies

Table 2 shows the methodological quality of all the included studies based on the Newcastle Ottawa Scale. All the included studies were awarded 7 or 8 stars: three out of five case-control studies and two out of four cohort studies were given 8. The mean score was 7.6 for case-control studies and 7.5 for cohort studies.

Dietary intake of omega-3 fatty acids and risk of endocrine-related gynecological cancer

As shown in Figure 1, overall, compared to the lowest intake of dietary omega-3 fatty acids, the highest intake was not associated with the risk of endocrine-related gynecological cancer in the meta-analysis of case-control studies (n=5) and cohort studies (n=3) (pOR/HR, 0.87; 95% CI, 0.73-1.04; I^2=67.2%). In the meta-analysis by types of study, dietary intake of omega-3 fatty acids was not associated with risk of endocrine-related gynecological cancer in cohort studies (pHR, 1.03; 95% CI, 0.63-1.67; I^2=81.9%; n=3), while a significantly decreased risk was found in the pooled analysis of case-control studies (pOR, 0.81; 95% CI, 0.67-0.98, I^2=55.7%, n=5). No publication bias was observed in the main analysis: the Begg's funnel plot was symmetrical, and the p for bias from the Egger's test was 0.41 (Supplementary figure 2). Further, there was no significant association between dietary intake of omega-3 fatty acids and endocrine-related gynecological cancer in the subgroup meta-analyses by study quality (low versus high), type of omega-3 fatty acids (ALA, EPA, DHA, and DPA), and type of cancer and type of study in each type of omega-3 fatty acids (Table 3 and Figure 2).

DISCUSSION

Summary of findings

The current study found that there was no significant association between dietary intake of omega-3 fatty acids and the risk of endocrine-related gynecological cancer overall, and in the pooled estimate of cohort studies, while food intake of omega-3 fatty acids was associated with the decreased risk of endocrine-related gynecological cancer in case-control studies.

Assessment of bias

The discrepancies in the effect of dietary intake of omega-3 fatty acids on the risk of these cancers between case-control studies and cohort studies might be associated with some important biases.[29] In general, case-control studies are more sensitive to selection bias and recall bias than prospective cohort studies.[29] Retrospective case-control studies require participants to recall their eating behaviors in which cancer patients might recall their dietary intakes differently from controls. In this context, the protective effect of the dietary intake of omega-3 fatty acids may be false findings since cancer patients tend to report lower consumption of omega-3 fatty acids than actual one, and healthy participants tend to stick with their regular healthy habits.[30] Selection bias may occur because controls from hospital-based case-control studies may not represent the general population.

Comparison with previous studies

Our findings are consistent with those from the previous meta-analyses that investigated the association between dietary intake of polyunsaturated fatty acids or fish intake and the risk of endocrine-related gynecological cancer. Qiu et al reported that polyunsaturated fat intake was not associated with the risk of ovarian cancer in the meta-analysis of case-control studies and cohort studies.[31] Also, Zhao et al found that there was no association between polyunsaturated fatty acid intake and the risk of endometrial cancer in the meta-analyses of case-control studies and cohort studies separately.[32] Also, Bandera et al suggested a positive association between fish intake, which is an important food source for omega-3 fatty acids, and endometrial cancer risk in the meta-analysis of case-control studies.[33]

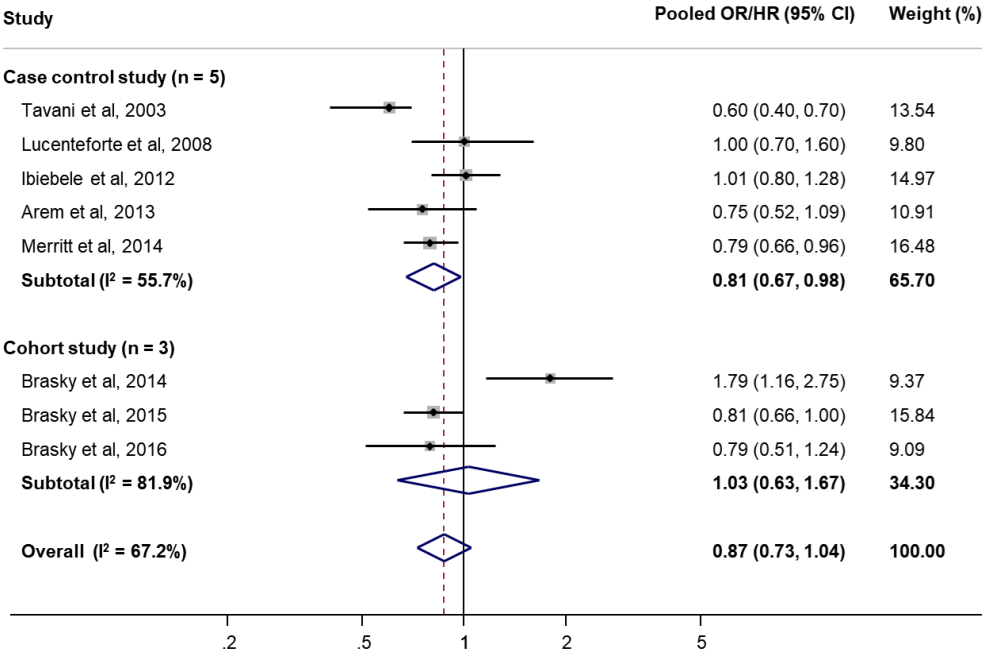


Figure 1. Dietary omega-3 fatty acids intake and risk of endocrine-related gynecological cancer in a random-effects meta-analysis of obse
ratio; CI, confidence interval.

Table 1. General characteristics of 10 observational studies included in the analysis

Study	Source of participants (Country)	Population (Follow-up period)	Cancer type	Type of dietary omega-3 fatty acids	OR or RR or HR (95% CI)	Adjusted variables
Case-control study (n=6)						
Bidoli et al, 2002 [15]	Multicentric Case-Control study (Italy)	1,031 cases/ 2,411 controls (1991-1999)	Ovarian cancer	ALA	OR: 0.8 (0.6-1.0)	Age, study center, year of interview, education, parity, oral contraceptive use, and energy intake
Tavani et al, 2003 [16]				Total omega-3 fatty acids	OR: 0.6 (0.4-0.7)	Age, study center, education, body mass index (BMI), energy intake, and parity
Lucenteforte et al, 2008 [17]	Case-Control study (Italy)	454 cases/ 908 controls (1992-2006)	Endometrial cancer	ALA	OR: 1.0 (0.7-1.6)	Age and study center, adjusted for year of interview, education, physical activity, BMI, history of diabetes, age at menarche, age at menopause, parity, oral contraceptives use, hormone replacement therapy use, and total energy intake
Ibiebele et al, 2012 [18]	Australian Ovarian Cancer Case-Control study (Australia)	1,366 cases/ 1,414 controls (2002-2005)	Ovarian cancer	ALA EPA DHA DPA Total omega-3 fatty acids	OR: 1.19 (0.93-1.52) OR: 0.87 (0.70-1.09) OR: 0.92 (0.74-1.15) OR: 1.06 (0.85-1.33) OR: 1.01 (0.80-1.28)	Age, education, BMI, smoking status, oral contraceptive use, parity, menopausal status, hormonal replacement therapy, total fat intake, total energy, and total ω-6 fatty acid intake
Arem et al, 2013 [22]	Population-Based Case-Control study (United States)	556 cases/ 533 controls (2004-2008)	Endometrial cancer	ALA EPA DHA Total omega-3 fatty acids	OR: 0.91 (0.63-1.32) OR: 0.57 (0.39-0.84) OR: 0.64 (0.44-0.94) OR: 0.75 (0.52-1.09)	Energy consumption, age, BMI, number of live births, menopausal status, oral contraceptive use, hypertension, smoking status, and race/ethnicity
Merritt et al, 2014 [20]	New England Case-control study (United States)	1,872 cases/ 1,978 controls (1992-2008)	Ovarian cancer	Total omega-3 fatty acids	OR: 0.79 (0.66-0.96)	Age, study center, study phase, number of pregnancies, oral contraceptive use, family history of ovarian cancer, and history of tubal ligation

Table 1. General characteristics of 10 observational studies included in the analysis (cont.)

Study	Source of participants (Country)	Population (Follow-up period)	Cancer type	Type of dietary omega-3 fatty acids	OR or RR or HR (95% CI)	Adjusted variables
Cohort study (n=4)						
Bertone et al, 2002 [14]	Nurses' Health Study cohort (United States)	80,258 nurses (1980-1996)	Ovarian cancer	ALA EPA DHA	RR: 1.00 (0.72-1.39) RR: 0.97 (0.64-1.48) RR: 0.86 (0.55-1.33)	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, tubal ligation, and smoking status
Brasky et al, 2014 [19]	VITamins And Lifestyle cohort (United States)	22,494 women (2000-2010)	Endometrial cancer	ALA EPA DHA EPA+DHA	HR: 0.85 (0.56-1.29) HR: 1.73 (1.14-2.63) HR: 1.66 (1.09-2.55) HR: 1.79 (1.16-2.75)	Age, race, education, BMI, pack-years of smoking, physical activity, alcohol consumption, age at menarche, age at first birth, age at menopause, parity, years of combined hormone therapy, years of estrogen-only therapy, years of oral contraceptive use, oophoerectomy, family history of uterine cancer, family history of ovarian cancer, history of diabetes, and total energy
Brasky et al, 2015 [3]	Women's Health Initiative Observational Study and Clinical Trial (United States)	87,360 postmenopausal women (1993-2010)	Endometrial cancer	ALA EPA DHA DPA EPA+DPA+DHA	HR: 0.96 (0.79-1.18) HR: 0.81 (0.65-1.01) HR: 0.77 (0.63-0.95) HR: 0.85 (0.69-1.05) HR: 0.81 (0.66-1.00)	Intervention assignment, US region, race, education, BMI, smoking, alcohol, physical activity, age at menarche, age at first birth, age at menopause, parity, duration of combined menopausal hormone therapy, duration of estrogen-alone hormone therapy, duration of oral contraceptive use, oophoerectomy status, family history of endometrial cancer, and history of diabetes
Brasky et al, 2016 [21]	Black Women's Health Study (United States)	47,602 African-American women (1995-2013)	Endometrial cancer	ALA EPA DHA DPA EPA+DPA+DHA	HR: 0.86 (0.56-1.33) HR: 0.72 (0.47-1.10) HR: 0.84 (0.54-1.30) HR: 0.88 (0.57-1.36) HR: 0.79 (0.51-1.24)	Age, time period, and total energy intake, US region, education, BMI, physical activity, alcohol consumption, smoking, fruit consumption, vegetable consumption, age at menarche, age at menopause, parity, age at first birth, duration of combined hormone therapy, duration of estrogen-alone hormone therapy, duration of oral contraceptive use, and diabetes

Table 2. Methodological quality of studies based on the Newcastle-Ottawa scale

Case-control study (n=6)	Selection			
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls
Bidoli et al, 2002 [15]	☆	☆	-	☆
Tavani et al, 2003 [16]	☆	☆	-	☆
Lucenteforte et al, 2008 [17]	☆	☆	-	☆
Ibiebele et al, 2012 [18]	☆	☆	☆	☆
Arem et al, 2013 [22]	☆	☆	☆	☆
Merritt et al, 2014 [20]	☆	☆	☆	☆
Cohort study (n=4)	Selection			
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	No present of outcomes of interest at start of the study
Bertone et al, 2002 [14]	-	☆	☆	☆
Brasky et al, 2014 [19]	☆	☆	☆	☆
Brasky et al, 2015 [3]	☆	☆	☆	☆
Brasky et al, 2016 [21]	-	☆	☆	☆

Case-control study (n=6)	Comparability	Expose			Total
	Comparability of cases and controls	Exposure ascertainment	Same ascertainment criteria for cases and controls	Non-response rate	
Bidoli et al, 2002 [15]	☆☆	☆	☆	-	7
Tavani et al, 2003 [16]	☆☆	☆	☆	-	7
Lucenteforte et al, 2008 [17]	☆☆	☆	☆	-	7
Ibiebele et al, 2012 [18]	☆☆	☆	☆	-	8
Arem et al, 2013 [22]	☆☆	☆	☆	-	8
Merritt et al, 2014 [20]	☆☆	☆	☆	-	8
Cohort study (n=4)	Comparability	Outcome			Total
	Comparability of cohorts	Assessment of outcome	Long follow-up enough for outcomes	Adequacy of follow-up of cohorts	
Bertone et al, 2002 [14]	☆☆	☆	☆	-	7
Brasky et al, 2014 [19]	☆☆	☆	☆	-	8
Brasky et al, 2015 [3]	☆☆	☆	☆	-	8
Brasky et al, 2016 [21]	☆☆	☆	☆	-	7

Table 3. Subgroup analysis by type of dietary omega-3 fatty acids and study quality

Factor	No. of Studies	Pooled OR/RR/HR (95% CI)	I^2 (%)
Methodological quality			
Low (score of 7 stars) [16,17,21]	3	0.76 (0.55-1.03)	52.7%
High (score of 8 stars) [3,18-20,22]	5	0.93 (0.75-1.66)	72.1%
Type of omega-3 fatty acids			
EPA [3,14,18-22]	6	0.88 (0.69-1.12)	69.6%
Endometrial cancer [3,19,21,22]	4	0.86 (0.58-1.30)	81.3%
Ovarian cancer [14,18]	2	0.89 (0.73-1.08)	71.5%
Case-control study [18,22]	2	0.73 (0.48-1.09)	71.4%
Cohort study [3,14,19,20]	4	0.98 (0.69-1.39)	73.7%
ALA [3,14,15,17-19,21,22]	8	0.96 (0.86-1.06)	39.8%
Endometrial cancer [3,17,19,21,22]	5	0.93 (0.81-1.08)	0.0%
Ovarian cancer [14,15,18]	3	0.99 (0.77-1.26)	58.6%
Case-control study [15,17,22]	4	0.97 (0.79-1.18)	39.8%
Cohort study [3,14,19,21]	4	0.94 (0.81-1.09)	0.0%
DHA [3,14,18,19,21,22]	6	0.89 (0.72-1.10)	61.6%
Endometrial cancer [3,19,21,22]	4	0.89 (0.63-1.28)	76.1%
Ovarian cancer [14,18]	2	0.91 (0.75-1.11)	0.0%
Case-control study [18,22]	2	0.79 (0.56-1.13)	61.9%
Cohort study [3,14,19, 21]	4	0.96 (0.69-1.35)	70.7%
DPA [3,18,21]	3	0.94 (0.81-1.08)	3.5%
Endometrial cancer [3,21]	2	0.86 (0.71-1.03)	0.0%
Ovarian cancer [18]	1	1.06 (0.85-1.33)	NA
Case-control study [18]	1	1.06 (0.85-1.33)	NA
Cohort study [3,21]	2	0.86 (0.71-1.03)	0.0%

OR: odds ratio; RR: relative risk; HR: hazard ratio; CI: confidence interval; ALA: alpha-linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; NA: not applicable.

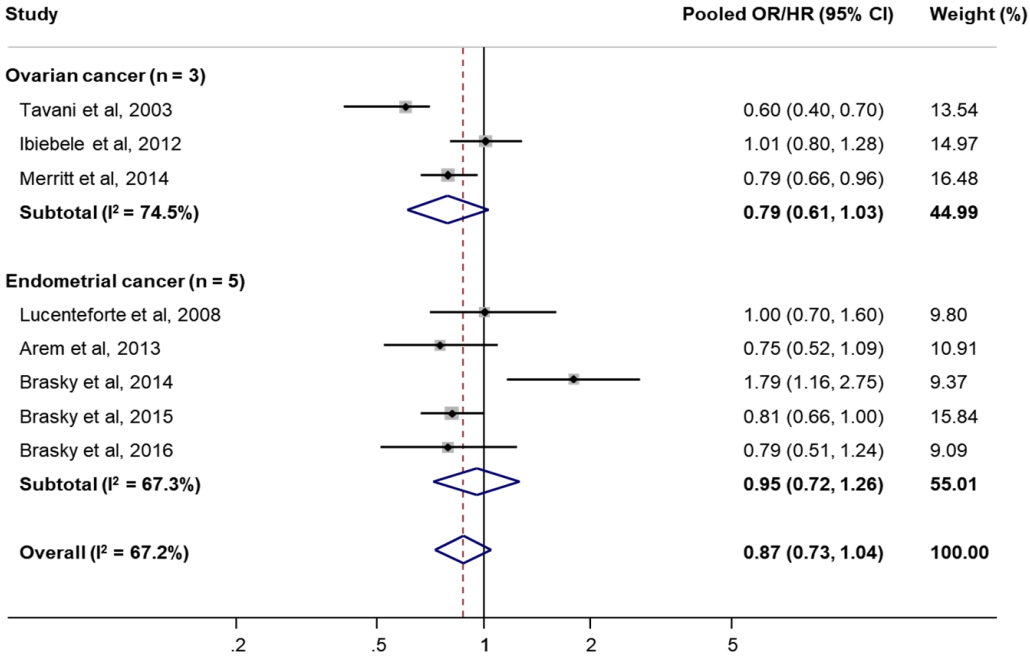


Figure 2. Dietary omega-3 fatty acids intake and risk of endocrine-related gynecological cancer in a random-effects meta-analysis of observational studies by type of cancer (n = 8). OR, odds ratio; HR, hazard ratio; CI, confidence interval.

Possible mechanisms

There are several hypotheses regarding the potential protective effect of omega-3 fatty acids on endocrine-related gynecological cancer. A nested case-control study reported that increasing concentrations of CRP, which is a marker of chronic systemic inflammation, was associated with an increased risk of ovarian cancer.[6] Another nested case-control study also suggested that CRP levels were positively associated with the risk of endometrial cancer.5 Regarding the anti-inflammatory and immunosuppressive properties of omega-3 fatty acids such as EPA and DHA Chapkin et al reported three main overarching mechanisms, including the modulation of the nuclear receptor activation, the inhibition of arachidonic acid-cyclooxygenase-derived eicosanoids, and the changing of the plasma membrane micro-organization (lipid rafts).[3,20] Regarding direct anti-carcinogenic mechanisms, previous preclinical studies using cancer cell lines and mice suggested that omega-3 fatty acids may reduce tumor cell proliferation, migration, and promote tumor cell apoptosis by inhibiting the mechanistic target of rapamycin (mTOR) complex 1 and 2 signaling, which is one of the major tar-

gets for the treatment of endometrial cancer.[35] Also, it has been reported that omega-3 fatty acids had anti-proliferative and anti-carcinogenic effects on epithelial ovarian cancer cell lines.[36,37] However, those anti-cancer effects of omega-3 effects were not observed in our meta-analysis of observational epidemiological studies.

Strengths and limitations

To the best of our knowledge, this is the first meta-analysis that reports the associations between dietary intake of omega-3 fatty acids and the risk of endocrine-related gynecological cancers. Our study has limitations. We included a relatively small number of individual studies with six case-control studies and four cohort studies. Thus, further large prospective cohort studies are warranted to confirm our findings. Also, our findings should be limited to dietary intake of omega-3 fatty acids from foods. We initially planned to evaluate the effects of omega-3 fatty acid supplements on the risk of endocrine-related gynecological cancer. However, only the VITAL study[19] reported the result in which source of omega-3 fatty acids is from diet plus supplements from three core databases (PubMed, Embase, and Cochrane Library).

Conclusion

In conclusion, given that generally prospective cohort studies give us a higher level of evidence than case-control studies, the current meta-analysis of observational studies suggests that there was no enough evidence to support the protective effect of food intake of omega-3 fatty acids on the risk of endocrine-related gynecological cancer such as endometrial cancer and ovarian cancer. Further larger prospective studies are warranted to confirm our findings.

Publisher's note

The publisher and editors acknowledge that this work has previously been published in the Journal Cancer Research and Treatment in 2019 (https://www.ecrt.org/journal/view.php?doi=10.4143/crt.2018.473) and retracted in January 2020 because of 'serious similarity' with 2015 Brasky et al's article (https://academic.oup.com/ajcn/article/101/4/824/4577552) (https://www.e-crt.org/journal/view.php?number=3057). The authors disputed the decision arguing that similarity was minor (three sentences in the introduction section similar to 2015 Brasky et al's article and duly cited). The present paper, a meta-analysis, makes due reference to Brasky et al's studies, provides perspective and merits publication.

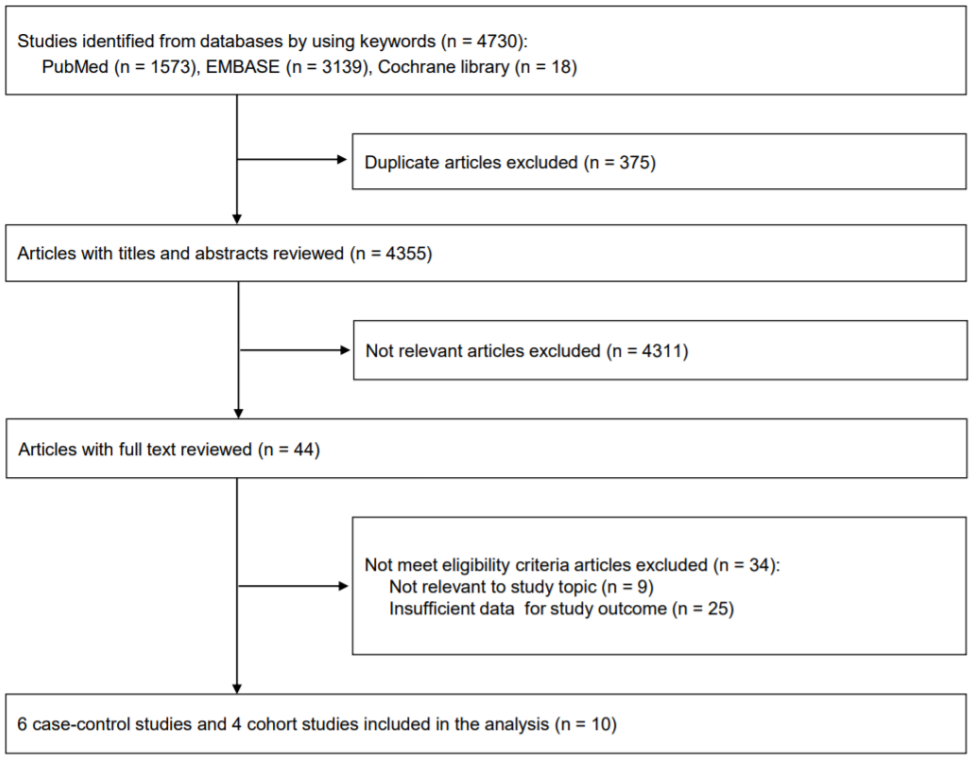
AUTHOR DISCLOSURES

We declare that we have no conflicts of interest. This study receives no funding.

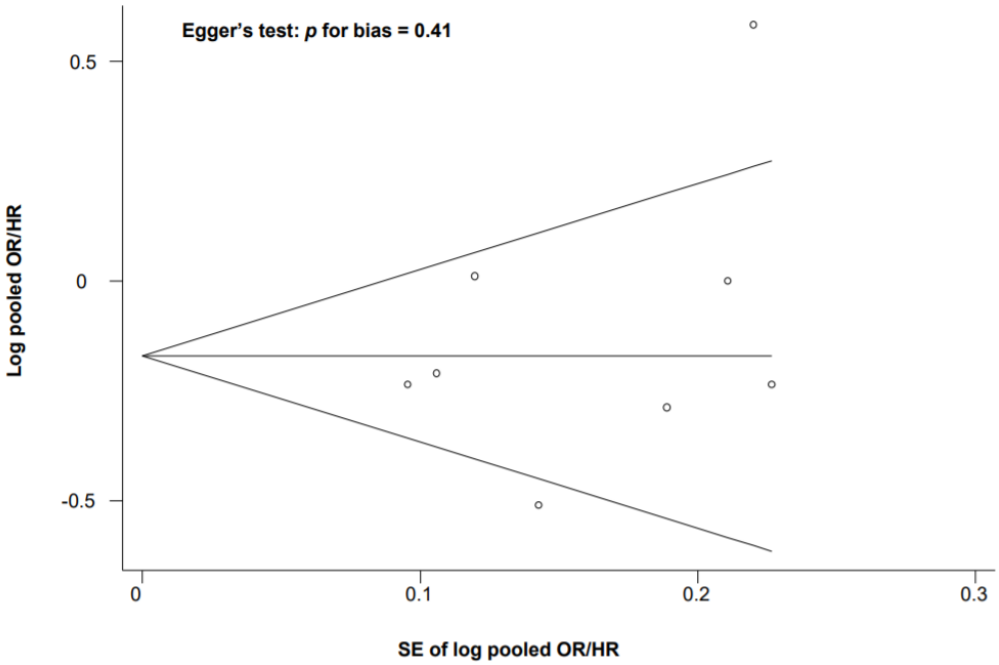
REFERENCES

1. Felix AS, Weissfeld JL, Stone RA, Bowser R, Chivukula M, Edwards RP et al. Factors associated with Type I and Type II endometrial cancer. Cancer Causes Control. 2010;21:1851-6. doi: 10.1007/s10552-010-9612-8.
2. Gibson DA, Simitsidellis I, Collins F, Saunders PT. Evidence of androgen action in endometrial and ovarian cancers. Endocr Relat Cancer. 2014;21:T203-18. doi: 10.1530/ERC-13-0551.
3. Brasky TM, Rodabough RJ, Liu J, Kurta ML, Wise LA, Orchard TS et al. Long-chain omega-3 fatty acid intake and endometrial cancer risk in the Women's Health Initiative. Am J Clin Nutr. 2015;101:824-34. doi: 10.3945/ajcn.114.098988.
4. Dossus L, Rinaldi S, Becker S, Lukanova A, Tjonneland A, Olsen A et al. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. Endocr Relat Cancer. 2010;17:1007-19. doi: 10.1677/ERC-10-0053.
5. Wang T, Rohan TE, Gunter MJ, Xue X, Wactawski-Wende J, Rajpathak SN et al. A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. Cancer Epidemiol Biomarkers Prev. 2011;20:971-7. doi: 10.1158/1055-9965.EPI-10-1222.
6. McSorley MA, Alberg AJ, Allen DS, Allen NE, Brinton LA, Dorgan JF et al. C-reactive protein concentrations and subsequent ovarian cancer risk. Obstet Gynecol. 2007;109:933-41. doi: 10.1097/01.AOG.0000257126.68803.03.
7. Verdoodt F, Friis S, Dehlendorff C, Albieri V, Kjaer SK. Non-steroidal anti-inflammatory drug use and risk of endometrial cancer: A systematic review and meta-analysis of observational studies. Gynecol Oncol. 2016;140:352-8. doi: 10.1016/j.ygyno.2015.12.009.
8. Murphy MA, Trabert B, Yang HP, Park Y, Brinton LA, Hartge P et al. Non-steroidal anti-inflammatory drug use and ovarian cancer risk: findings from the NIH-AARP Diet and Health Study and systematic review. Cancer Causes Control. 2012;23:1839-52. doi: 10.1007/s10552-012-0063-2.
9. Kantor ED, Lampe JW, Vaughan TL, Peters U, Rehm CD, White E. Association between use of specialty dietary supplements and C-reactive protein concentrations. Am J Epidemiol. 2012;176:1002-13. doi: 10.1093/aje/kws186.
10. Micallef MA, Munro IA, Garg ML. An inverse relationship between plasma n-3 fatty acids and C-reactive protein in healthy individuals. Eur J Clin Nutr. 2009;69:1154-6. doi: 10.1038/ejcn.2009.20.
11. Ebrahimi M, Ghayour-Mobarhan M, Rezaiean S, Hoseini M, Parizade SM, Farhoudi F et al. Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity. Acta Cardiol. 2009;64:321-7. doi: 10.2143/AC.64.3.2038016.
12. Malekshahi Moghadam A, Saedisomeolia A, Djalali M, Djazayery A, Pooya S, Sojoudi F. Efficacy of omega-3 fatty acid supplementation on serum levels of tumour necrosis factor-alpha, C-reactive protein and interleukin-2 in type 2 diabetes mellitus patients. Singapore Med J. 2012;53:615-9.
13. Micallef MA, Garg ML. Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals. Atherosclerosis. 2009;204:476-82. doi: 10.1016/j.atherosclerosis.2008.09.020.
14. Bertone ER, Rosner BA, Hunter DJ, Stampfer MJ, Speizer FE, Colditz GA et al. Dietary fat intake and ovarian cancer in a cohort of US women. Am J Epidemiol. 2002;156:22-31. doi: 10.1093/aje/kwf008.
15. Bidoli E, La Vecchia C, Montella M, Maso LD, Conti E, Negri E, Scarabelli C et al. Nutrient intake and ovarian cancer: an Italian case-control study. Cancer Causes Control. 2002;13:255-61. doi: 10.1023/a:1015047625060.
16. Tavani A, Pelucchi C, Parpinel M, Negri E, Franceschi S, Levi F et al. n-3 polyunsaturated fatty acid intake and cancer risk in Italy and Switzerland. Int J Cancer. 2003;105:113-6. doi: 10.1002/ijc.11018.
17. Lucenteforte E, Talamini R, Montella M, Dal Maso L, Tavani A, Deandrea S et al. Macronutrients, fatty acids and

cholesterol intake and endometrial cancer. Ann Oncol. 2008; 19:168-72. doi: 10.1093/annonc/mdm446.
18. Ibiebele TI, Nagle CM, Bain CJ, Webb PM. Intake of omega-3 and omega-6 fatty acids and risk of ovarian cancer. Cancer Causes Control. 2012;23:1775-83. doi: 10.1007/s10552-012-0053-4.
19. Brasky TM, Neuhouser ML, Cohn DE, White E. Associations of long-chain omega-3 fatty acids and fish intake with endometrial cancer risk in the VITamins And Lifestyle cohort. Am J Clin Nutr. 2014;99:599-608.
20. Merritt MA, Cramer DW, Missmer SA, Vitonis AF, Titus LJ, Terry KL. Dietary fat intake and risk of epithelial ovarian cancer by tumour histology. Br J Cancer. 2014;110: 1392-401.
21. Brasky TM, Sponholtz TR, Palmer JR, Rosenberg L, Ruiz-Narvaez EA, Wise LA. Associations of dietary long-chain omega-3 polyunsaturated fatty acids and fish consumption with endometrial cancer risk in the Black Women's Health Study. Am J Epidemiol. 2016;183:199-209. doi: 10.1093/aje/kwv231.
22. Arem H, Neuhouser ML, Irwin ML, Cartmel B, Lu L, Risch H et al. Omega-3 and omega-6 fatty acid intakes and endometrial cancer risk in a population-based case-control study. Eur J Nutr. 2013; 52:1251-60. doi: 10.1007/s00394-012-0436-z.
23. Wells GA, Shea B, Connell DO, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited 2017/09/19]; Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp/.
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.
25. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. [cited 2017/09/19]; Available at http://www.handbook.cochrane.org/.
26. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1:97-111. doi: 10.1002/jrsm.12.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34. doi: 10.1136/bmj.315.7109.629.
28. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med. 2001; 20:641-54. doi: 10.1002/sim.698.
29. Hammer GP, du Prel JB, Blettner M. Avoiding bias in observational studies: part 8 in a series of articles on evaluation of scientific publications. Dtsch Arztebl Int. 2009;106:664-8. doi: 10.3238/arztebl.2009.0664.
30. Giovannucci E, Stampfer MJ, Colditz GA, Manson JE, Rosner BA, Longnecker M et al. A comparison of prospective and retrospective assessments of diet in the study of breast cancer. Am J Epidemiol. 1993;137:502-11. doi: 10.1093/oxfordjournals.aje.a116703.
31. Qiu W, Lu H, Qi Y, Wang X. Dietary fat intake and ovarian cancer risk: a meta-analysis of epidemiological studies. Oncotarget. 2016;7:37390-406. doi: 10.18632/oncotarget.8940.
32. Zhao J, Lyu C, Gao J, Du L, Shan B, Zhang H et al. Dietary fat intake and endometrial cancer risk: A dose response meta-analysis. Medicine (Baltimore). 2016;95:e4121. doi: 10.1097/MD.0000000000004121.
33. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: a systematic literature review and meta-analysis. Cancer Causes Control. 2007; 18:967-88. doi: 10.1007/s10552-007-9038-0.
34. Chapkin RS, Kim W, Lupton JR, McMurray DN. Dietary docosahexaenoic and eicosapentaenoic acid: emerging mediators of inflammation. Prostaglandins Leukot Essent Fatty Acids. 2009;81:187-91. doi: 10.1016/j.plefa.2009.05.010.
35. Zheng H, Tang H, Liu M, He M, Lai P, Dong H et al. Inhibition of endometrial cancer by n-3 polyunsaturated fatty acids in preclinical models. Cancer Prev Res (Phila). 2014;7:824-34. doi: 10.1158/1940-6207.CAPR-13-0378-T.
36. Sharma A, Belna J, Logan J, Espat J, Hurteau JA. The effects of omega-3 fatty acids on growth regulation of epithelial ovarian cancer cell lines. Gynecol Oncol. 2005;99: 58-64. doi: 10.1016/j.ygyno.2005.05.024.
37. Wan XH, Fu X, Ababaikeli G. Docosahexaenoic acid induces growth suppression on epithelial ovarian cancer cells more effectively than eicosapentaenoic acid. Nutr Cancer. 2016;68:320-7. doi: 10.1080/01635581.2016.1142581.



Supplementary figure 1. Flow diagram for selection of relevant studies.



Supplementary figure 2. Begg's funnel plots and Egger's test for publication bias. OR: odd ratio; HR: hazard ratio; SE: standard error.