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Dietary omega-3 fatty acids and endometrial cancer risk in the Epidemiology of Endometrial Cancer Consortium: An individual-participant meta-analysis

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Abbreviations: AA, Arachidonic acid; ALA, Alpha-linolenic acid; BWHS, Black Women's Health Study; BMI, Body mass index; CI, Confidence interval; DHA, Docosahexaenoic acid; DPA, Docosapentaenoic acid; EPA, Eicosapentaenoic acid; E2C2, Epidemiology of Endometrial Cancer Consortium; FFQ, Food frequency questionnaire; HR, Hazard ratio; IPD, Individual-participant data; LA, Linoleic acid; LCn3, Long-chain omega-3; OR, Odds ratio; n6, Omega-6; PUFA, Polyunsaturated fatty acid; VITAL, Vitamins and Lifestyle cohort study; WHI, Women's Health Initiative.

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HIGHLIGHTS

- We conducted an individual-participant data meta-analysis of dietary omega-3 fatty acids and endometrial cancer risk.
- Data were obtained from 12 prospective cohort studies.
- Small, positive associations between dietary omega-3 fatty acids and endometrial cancer were observed overall.
- Stronger, moderate positive associations were observed among participants with body mass indices ≥25 kg/m^2.

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ABSTRACT

Background. Limited data from prospective studies suggest that higher dietary intake of long-chain omega-3 polyunsaturated fatty acids (LCn3PUFA), which hold anti-inflammatory properties, may reduce endometrial cancer risk; particularly among certain subgroups characterized by body mass and tumor pathology.

Materials and methods. Data from 12 prospective cohort studies participating in the Epidemiology of Endometrial Cancer Consortium were harmonized as nested case-control studies, including 7268 endometrial cancer cases and 26,133 controls. Habitual diet was assessed by food frequency questionnaire, from which fatty acid intakes were estimated. Two-stage individual-participant data mixed effects meta-analysis estimated adjusted odds ratios (OR) and 95% confidence intervals (CI) through logistic regression for associations between study-specific energy-adjusted quartiles of LCn3PUFA and endometrial cancer risk.

Results. Women with the highest versus lowest estimated dietary intakes of docosahexaenoic acid, the most abundant LCn3PUFA in diet, had a 9% increased endometrial cancer risk (Quartile 4 vs. Quartile 1: OR 1.09, 95% CI: 1.01–1.19; *P* trend = 0.04). Similar elevated risks were observed for the summary measure of total LCn3PUFA (OR 1.07, 95% CI: 0.99–1.16; *P* trend = 0.06). Stratified by body mass index, higher intakes of LCn3PUFA were associated with 12–19% increased endometrial cancer risk among overweight/obese women and no increased risk among normal-weight women. Higher associations appeared restricted to White women. The results did not differ by cancer grade.

Conclusion. Higher dietary intakes of LCn3PUFA are unlikely to reduce endometrial cancer incidence; rather, they may be associated with small to moderate increases in risk in some subgroups of women, particularly overweight/obese women.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States and the fourth most common cancer diagnosed in women [1]. Endometrial cancer is an increasing public health challenge. Incidence and mortality rates are rising for all groups [2], although increases among Black women, who are more often diagnosed with aggressive disease and have substantially higher mortality rates than White women [3–5] are particularly concerning. Endometrial cancer is curable when detected early and the mortality rate remains relatively low in White women compared to other cancers. However, other factors, including higher mortality rates [3–6], $3 billion annually in uterine cancer care expenditure [7,8], patient anxiety [9,10], and surgical complications [11] must be considered when evaluating endometrial cancer's impact.

Increasing evidence suggests that interplay between unopposed estrogens and inflammatory signaling are important in endometrial cancer etiology [12,13]. Long-chain omega-3 (LCn3) polyunsaturated fatty acids (PUFA), which derive primarily from oily fish, are anti-inflammatory [14–18] and may reduce de novo estrogen signaling through inhibition of synthesis of both prostaglandins and aromatase [19,20]. Prospective data are currently limited to three studies and among them results have been inconsistent; however, each reported that dietary intakes of LCn3PUFA may be associated with reduced endometrial cancer risk among leaner women and possibly for low-grade cancers [21–23]. Herein, we provide the results of an individual-participant data (IPD) meta-analysis utilizing data from 12 diverse prospective studies, 11 of which were included in the Epidemiology of Endometrial Cancer Consortium (E2C2), to examine the association between dietary LCn3PUFA intake and endometrial cancer risk more precisely and comprehensively.

2. Methods

2.1. E2C2: The epidemiology of Endometrial Cancer Consortium

Established in 2006, the E2C2 is an international consortium of 38 studies that was designed specifically to pool resources to study genetic, reproductive, and behavioral risk factors of endometrial cancer. Included in this analysis were 11 prospective cohort studies that participated in the E2C2 (Supplemental Table 1). The Women's Health Initiative (WHI) [24–27] prospective study, which is not a formal member of the consortium, also contributed data to this analysis. Separately, we also analyzed data from five population-based case-control studies within the E2C2 for comparison with results from prospective analyses (see Supplemental Tables 4–8). Compared to cohort studies where dietary data were collected long before the diagnosis of cancer, case-control studies are potentially more susceptible to recall bias on diet due to the disease status. All studies were approved by the relevant research ethics committees and all participants gave informed consent. This report follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses-Individual Participant Data (PRISMA-IPD) reporting guideline [28].

The E2C2 data harmonization process has been described in detail elsewhere [29]. Briefly, all cohort studies were structured as nested case-control studies and their data provided to the consortium's coordinating center at Memorial Sloan Kettering Cancer Center (New York, NY). Up to four at-risk controls were randomly selected from their underlying cohorts using incidence density sampling and matched to cases on year of birth, cohort entry date, and other study-specific criteria as appropriate. Controls who had a hysterectomy or a personal history of endometrial cancer by the time of selection were ineligible for selection. Cases were defined as incident, first primary diagnoses of

endometrial carcinoma (ICD-O topography codes C54 and C55.9) and were identified through annual linkage to state or national cancer registries, or through a combination of self-report confirmed through medical records review, linkage to cancer registries, or to national death indices. Using the same guidelines as for prospective studies participating in the E2C2, we selected incident endometrial cancer cases and at-risk controls from the WHI matched on age and clinical trial enrollment, and harmonized participants' data in accordance with the E2C2's harmonization procedures.

2.2. Eligibility criteria

Beginning with 43,909 women from 17 studies with available dietary data, we made the following exclusions (Fig. 1): uterine cancers of non-epithelial origin (e.g., sarcomas; $n = 149$); prior cancer other than non-melanoma skin cancer ($n = 1159$); unrealistic caloric intakes (<500 or >5000 kcal/day; $n = 2181$); and missing LCn3PUFA data ($n = 26$), age ($n = 4$), or controls without a matched case due to above exclusions ($n = 1168$). After exclusions there were 39,222 participants available for analysis. Data from 33,243 women ($n = 72,212$ cases and 26,031 controls) participating in prospective studies are given herein, and an additional 5979 ($n = 2752$ cases and 3227 controls) are presented in Supplemental Tables 4–8.

2.3. Data collection

De-identified baseline data from E2C2 participating studies were centrally collected and harmonized at Memorial Sloan Kettering Cancer Center. Baseline data from the WHI were separately obtained and harmonized at the WHI Midwest Regional Coordinating Center at The Ohio State University (Columbus, OH). Extensive data on demographics and exposures including age, self-identified race, education, body mass index (BMI; kg/m^2), reproductive variables, menopausal status, use of exogenous hormones, smoking, alcohol consumption, medical history, and physical activity were collected and harmonized [30,31]. In addition to risk factor data, each study has contributed, where available, clinical data for endometrial cancer cases, including tumor histology (derived from pathology reports, registry data, or both) and grade [29].

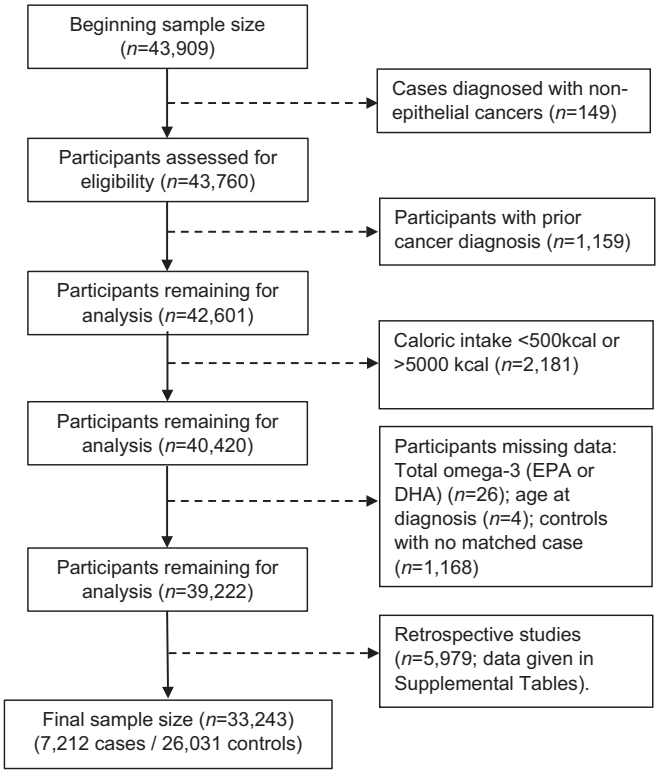

Fig. 1. Flowchart of sample selection from initial 17 E2C2 studies that made dietary data available.

2.4. Dietary assessment

Diet was assessed in the cohorts at their respective baselines using self-administered semi-quantitative food frequency questionnaires (FFQs). FFQs included those developed by Block et al. [32], the National Institutes of Health [33], the Women's Health Initiative [34], and Willet et al. [35] (Supplemental Table 1). Within the US, several studies (e.g., the Multiethnic Cohort Study [36] and Southern Community Cohort Study [37]) developed and validated FFQs for specific populations. Studies performed outside of the US developed and validated their own FFQs [38–45]. Fatty acids and energy intake were estimated by the individual studies using country-specific nutrient tables, which give estimates for the nutrient composition of food items, and diet calculation software (e.g., National Cancer Institute's Diet*Calc [46] or University of Minnesota's Nutrient Data System for Research [47]). Participant-level intakes of total energy (kcal/day), omega-3 fatty acids (alpha-linolenic [ALA], eicosapentaenoic [EPA], docosapentaenoic [DPA], and docosahexaenoic acids [DHA]), and omega-6 fatty acids (linoleic [LA] and arachidonic acids [AA]) were obtained from each participating study and harmonized with the E2C2 core dataset. Summary variables of total LCn3PUFA (EPA + DPA + DHA, or as EPA + DHA in ORDET and the Netherlands Cohort Study on Diet and Cancer) and total omega-6 (n6) fatty acids (LA + AA) were calculated. Fatty acids were energy-adjusted using the nutrient residual method [48], and categorized into study-specific quartiles determined from studies' whole populations. Therefore, quartile ranges given in tables represent energy-adjusted milligrams per day of intake. Intakes of LCn3PUFA from dietary supplements were not available for study. Categorizing dietary fatty acids using study-specific rather than overall quartiles is recommended for reducing error from different measurement and nutrient-estimation methods utilized across studies [49].

2.5. Tumor histology

Among 7212 endometrial cancer cases, tumor histology data were available for 6002 (83%). We classified tumors based on grade: low-grade tumors ($n = 4595$) were grades 1 and 2 endometrioid adenocarcinomas and endometrioid adenocarcinomas not otherwise specified; high-grade tumors ($n = 1322$) were grade 3 endometrioid adenocarcinomas and adenocarcinomas not otherwise specified, and serous adenocarcinomas, clear cell adenocarcinomas, mixed cell adenocarcinomas, or papillary adenocarcinomas [50]. Tumors with rarer histologies (e.g., squamous cell carcinomas, and neuroendocrine carcinomas; $n = 85$) as well as those missing pathology data ($n = 1266$) were included in the overall models but not included in models evaluating risk of endometrial cancers classified by grade.

2.6. Statistical methods

Across all prospective studies, we summarize the individual participant characteristics, including demographics, medical history, comorbidities, and lifestyle behaviors by endometrial cancer status. Synthesis of IPD across all studies utilized a two-stage meta-analysis approach. This approach allowed the matched sets of the nested case-control designs to be accounted for when available (2 studies) via conditional logistic regression, and with logistic regression when not available (10 studies), with random effects using a restricted maximum likelihood to account for clustering of individuals within studies. Models estimated odds ratios (OR) and 95% confidence intervals (CI) of endometrial cancer for each study-specific quartile relative to the

Table 1
Selected characteristics of participants among 12 prospective studies in the E2C2 consortium, stratified on endometrial cancer status, $n = 33{,}243$.

Characteristic	Cases, n (%), $n = 7212$	Controls, n (%), $n = 26{,}031$
Age, mean (SD)	66.34 (8.69)	68.09 (9.09)
Education		
≤High school	1891 (26.22)	6690 (25.70)
Some college	3118 (43.23)	11,369 (43.67)
College or advanced degree	2110 (29.26)	7653 (29.40)
Missing	93 (1.29)	319 (1.23)
Race		
Asian/Pacific Islander	439 (6.09)	1566 (6.02)
Black	623 (8.64)	2554 (9.81)
White	6072 (84.19)	21,696 (83.35)
Other	45 (0.62)	171 (0.66)
Missing	33 (0.46)	44 (0.17)
Body mass index (kg/m^2)		
<18.5	63 (0.87)	350 (1.34)
18.5–24.9	2286 (31.70)	11,313 (43.46)
25.0–29.9	2055 (28.49)	8494 (32.63)
30.0–34.9	1364 (18.91)	3464 (13.31)
35.0–39.9	699 (9.69)	1271 (4.88)
≥40.0	627 (8.69)	695 (2.67)
Missing	118 (1.64)	444 (1.71)
Smoking status		
Never smoker	4028 (55.85)	13,402 (51.48)
Former smoker	2373 (32.90)	8868 (34.07)
Current smoker	703 (9.75)	3339 (12.83)
Missing	108 (1.50)	422 (1.62)
Pack-years of smoking		
Never smoker	4028 (55.85)	13,405 (51.50)
0.1–3.0	359 (4.98)	1248 (4.79)
3.1–19.0	886 (12.29)	3180 (12.22)
>19.0	883 (12.24)	3453 (13.26)
Missing	1056 (14.64)	4745 (18.23)
Alcohol intake (g/week)		
0	2337 (32.40)	7763 (29.82)
0.1–14.0	2486 (34.47)	8948 (34.37)
14.1–98.0	1299 (18.01)	4906 (18.85)
>98.0	465 (6.45)	1950 (7.49)
Missing	625 (8.67)	2464 (9.47)
Age at menarche		
≤10	401 (5.56)	1188 (4.56)
11–12	3198 (44.34)	10,810 (41.53)
13–14	2937 (40.72)	11,109 (42.68)
≥15	607 (8.42)	2718 (10.44)
Missing	69 (0.96)	206 (0.79)
Parity		
Nulliparous	1146 (15.89)	3221 (12.37)
1	763 (10.58)	2636 (10.13)
2	1820 (25.24)	6711 (25.78)
3	1669 (23.14)	6574 (25.25)
4	805 (11.16)	3288 (12.63)
≥5	608 (8.43)	2774 (10.66)
Missing	401 (5.56)	827 (3.18)
Age at first birth		
Nulliparous	1146 (15.89)	3221 (12.37)
≤19	831 (11.52)	3454 (13.27)
20–29	3789 (52.54)	14,447 (55.50)
≥30	479 (6.64)	2001 (7.69)
Missing	967 (13.41)	2908 (11.17)
Menopausal status		
Pre-menopausal	593 (8.22)	1652 (6.35)
Peri-menopausal	1680 (23.29)	7025 (26.99)
Post-menopausal	4353 (60.36)	16,159 (62.08)
Missing	586 (8.13)	1195 (4.59)
Oral contraceptive use		
No	4219 (58.50)	13,885 (53.34)
Yes	2543 (35.26)	10,791 (41.45)
Missing	450 (6.24)	1355 (5.21)
Months of oral contraceptive use		
No use	4219 (58.50)	13,885 (53.34)
0.1–2.5	579 (8.03)	2193 (8.42)
2.6–29.5	609 (8.44)	1909 (7.33)
29.6–83.0	535 (7.42)	2369 (9.10)
>83.0	544 (7.54)	3003 (11.54)
Missing	726 (10.07)	2672 (10.26)
Hormone therapy use		
No	3584 (46.69)	13,928 (53.51)
Yes	3011 (41.75)	10,820 (41.57)
Missing	617 (8.56)	1283 (4.93)
Prevalent diabetes		
No	6571 (91.11)	24,430 (93.85)
Yes	629 (8.72)	1574 (6.05)
Missing	12 (0.17)	27 (0.10)
Prevalent hypertension		
No	4095 (56.78)	15,745 (60.49)
Yes	2405 (33.35)	7218 (27.73)
Missing	712 (9.87)	3068 (11.79)

first quartile. Tests for linear trend were calculated by treating quartiles of fatty acid variables as ordinal score variables in regression models. Models were adjusted at minimum for age, study, BMI, and energy intake, and further included risk factors determined a priori from the literature where possible [51,52]. Fully adjusted models additionally adjusted for race, smoking status, alcohol, menopausal status, ages at menarche and first birth, use of menopausal hormone therapy, duration of oral contraceptive use, and histories of diabetes and hypertension. A category for missing values was created for categorical covariates (categorized as given in Table 1). Secondary analyses explored the associations of dietary PUFA intake with endometrial cancer risk within subgroups of participants characterized by race (Asian/Pacific Islander, Black, White; see Supplemental Table 3) and body size (BMI < 25 and ≥25 kg/m^2). Exploratory models examined associations between dietary PUFA intakes and endometrial cancers characterized by their histology (low-grade endometrial cancer, high-grade endometrial cancer vs. controls) through IPD two-stage mixed effects multinomial regression models. Heterogeneity between studies was summarized via I^2 and the estimated between study variance summarized via τ^2 [53,54]. Descriptive analyses and data manipulation were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Two-stage IPD mixed effect meta-analyses were estimated using Stata version 16.1 (StataCorp LLC, College Station, TX, USA) with the ipdmetan command [55]. All *P* values and 95% CI are two-sided and presented at the nominal level.

3. Results

Participants included in the IPD meta-analysis are described in Table 1, stratified by endometrial cancer status. Compared to controls, endometrial cancer cases had greater BMI, began menstruating earlier, and had fewer children. Differences between the groups by participants' education, race, smoking history and alcohol intake, use of exogenous hormones (i.e., oral contraceptives and menopausal hormone therapy), and medical histories of diabetes or hypertension were small.

Mean energy-adjusted total LCn3PUFA intakes, quartile cut-points, and interquartile ranges for each study are given in Supplemental Table 1. Mean intakes ranged from 84.21 to 395.73 mg/d, with the highest intakes observed among participants of the two Swedish cohort studies.

We present associations of estimated dietary PUFA intake and endometrial cancer risk derived from IPD meta-analysis across 12 prospective studies participating in the E2C2 consortium in Table 2. Participants who consumed the most DHA (quartile 4) in their diets had slightly elevated endometrial cancer risk (fully adjusted OR 1.09, 95% CI: 1.01–1.19; *P* trend = 0.04) relative to those who consumed the least (quartile 1). A similar, slightly elevated risk was observed for total LCn3PUFA intake (OR 1.07, 95% CI: 0.99–1.16; *P* trend = 0.06) and for DPA (OR 1.07, 95% CI: 0.98–1.17; *P* trend = 0.05). No associations were observed for intakes of EPA or the shorter-chain n3PUFA ALA, nor for intakes of n6PUFA. Results were unchanged when

Table 2
Individual-participant data meta-analysis of dietary polyunsaturated fatty acid intake in relation to endometrial cancer risk among 12 prospective cohort studies, n = 33,243.

	Energy-adjusted study-specific quartiles[a]				
Fatty acid (lipid number)	1	2	3	4	*P* trend
Omega-3					
α-linolenic acid (18:3n3; ALA)					
OR (95% CI)[b]	1.00 referent	1.04 (0.95, 1.14)	0.99 (0.91, 1.07)	0.97 (0.88, 1.07)	0.412
OR (95% CI)[c]	1.00 referent	1.05 (0.96, 1.16)	1.02 (0.94, 1.11)	0.99 (0.89, 1.10)	0.703
Eicosapentaenoic acid (20:5n3; EPA)					
OR (95% CI)[b]	1.00 referent	0.97 (0.90, 1.05)	1.02 (0.94, 1.11)	1.04 (0.96, 1.13)	0.191
OR (95% CI)[c]	1.00 referent	0.98 (0.90, 1.06)	1.03 (0.95, 1.12)	1.05 (0.97, 1.14)	0.112
Docosapentaenoic acid (22:5n3; DPA)[c]					
OR (95% CI)[b]	1.00 referent	0.97 (0.90, 1.05)	1.06 (0.98, 1.15)	1.06 (0.97, 1.16)	0.073
OR (95% CI)[c]	1.00 referent	0.98 (0.90, 1.06)	1.06 (0.98, 1.15)	1.07 (0.98, 1.17)	0.054
Docosahexaenoic acid (22:6n3; DHA)					
OR (95% CI)[b]	1.00 referent	1.05 (0.97, 1.14)	1.06 (0.98, 1.15)	1.08 (0.99, 1.17)	0.076
OR (95% CI)[c]	1.00 referent	1.07 (0.99, 1.16)	1.07 (0.99, 1.16)	1.09 (1.01, 1.19)	0.042
Total long-chain omega-3 (EPA + DPA + DHA)[d]					
OR (95% CI)[b]	1.00 referent	1.00 (0.93, 1.08)	1.04 (0.96, 1.13)	1.06 (0.98, 1.15)	0.097
OR (95% CI)[c]	1.00 referent	1.01 (0.93, 1.10)	1.06 (0.97, 1.14)	1.07 (0.99, 1.16)	0.059
Omega-6					
Linoleic acid (18:2n6; LA)					
OR (95% CI)[b]	1.00 referent	1.04 (0.96, 1.12)	1.05 (0.97, 1.14)	1.02 (0.94, 1.10)	0.621
OR (95% CI)[c]	1.00 referent	1.04 (0.96, 1.13)	1.06 (0.98, 1.15)	1.03 (0.95, 1.11)	0.483
Arachidonic acid (20:4n6; AA)					
OR (95% CI)[b]	1.00 referent	0.99 (0.89, 1.10)	1.03 (0.94, 1.13)	1.01 (0.92, 1.10)	0.688
OR (95% CI)[c]	1.00 referent	0.99 (0.88, 1.11)	1.05 (0.95, 1.16)	1.02 (0.93, 1.12)	0.411
Total omega-6 (LA + AA)					
OR (95% CI)[b]	1.00 referent	1.03 (0.95, 1.11)	1.05 (0.97, 1.14)	1.02 (0.95, 1.10)	0.515
OR (95% CI)[c]	1.00 referent	1.03 (0.95, 1.12)	1.06 (0.98, 1.15)	1.03 (0.95, 1.12)	0.374

[a] Quartile cut-points for each individual study are given in Supplemental Table 1.
[b] Adjusted for age, study, education, body mass index, and total energy.
[c] Adjusted for age, study, education, body mass index, race, smoking status, alcohol, menopausal status, age at menarche, age at first birth, parity, any use of hormone therapy, duration of oral contraceptive use, history of diabetes, history of hypertension, energy intake. For these adjusted models, between study variability, measured by τ^2, had a median value of 0 and ranged from 0 to 0.015. The I^2 for heterogeneity ranged between 0 and 41%, with a median value of 0.
[d] ORDET and the Netherlands Cohort Study on Diet and Cancer did not measure DPA; total long-chain omega-3 fatty acids are calculated as EPA + DHA for these studies.

Table 3
Individual-participant data meta-analysis of dietary polyunsaturated fatty acid intake in relation to endometrial cancer risk stratified by body mass index, *n* = 33,243.

	OR (95% CI)[a,b,c] Energy-adjusted study-specific quartiles				
Fatty acid (lipid number)	1	2	3	4	*P* trend
Omega-3					
α-linolenic acid (18:3n3; ALA)					
<25 kg/m^2	1.00 referent	1.06 (0.92, 1.21)	1.04 (0.90, 1.19)	0.98 (0.83, 1.15)	0.770
≥25 kg/m^2	1.00 referent	1.08 (0.97, 1.20)	1.04 (0.93, 1.15)	1.04 (0.94, 1.16)	0.668
Eicosapentaenoic acid (20:5n3; EPA)					
<25 kg/m^2	1.00 referent	0.91 (0.80, 1.05)	0.94 (0.82, 1.08)	1.00 (0.87, 1.15)	0.819
≥25 kg/m^2	1.00 referent	1.04 (0.94, 1.16)	1.10 (0.99, 1.22)	1.12 (1.01, 1.24)	0.019
Docosapentaenoic acid (22:5n3; DPA)[c]					
<25 kg/m^2	1.00 referent	1.00 (0.87, 1.15)	1.08 (0.94, 1.24)	0.97 (0.84, 1.11)	0.926
≥25 kg/m^2	1.00 referent	0.99 (0.89, 1.10)	1.06 (0.95, 1.18)	1.15 (1.04, 1.28)	0.003
Docosahexaenoic acid (22:6n3; DHA)					
<25 kg/m^2	1.00 referent	0.96 (0.84, 1.10)	1.02 (0.89, 1.17)	1.00 (0.87, 1.15)	0.778
≥25 kg/m^2	1.00 referent	1.16 (1.05, 1.29)	1.13 (1.02, 1.26)	1.19 (1.08, 1.32)	0.003
Total long-chain omega-3 (EPA + DPA + DHA)[c,d]					
<25 kg/m^2	1.00 referent	0.96 (0.87, 1.14)	1.04 (0.90, 1.19)	1.00 (0.87, 1.15)	0.875
≥25 kg/m^2	1.00 referent	1.06 (0.96, 1.18)	1.10 (0.99, 1.22)	1.16 (1.05, 1.29)	0.004
Omega-6					
Linoleic acid (18:2n6; LA)					
<25 kg/m^2	1.00 referent	1.08 (0.93, 1.24)	1.07 (0.93, 1.22)	1.11 (0.97, 1.27)	0.171
≥25 kg/m^2	1.00 referent	1.00 (0.89, 1.11)	1.06 (0.96, 1.18)	0.99 (0.89, 1.09)	0.916
Arachidonic acid (20:4n6; AA)					
<25 kg/m^2	1.00 referent	1.04 (0.91, 1.18)	1.08 (0.94, 1.23)	0.99 (0.82, 1.18)	0.993
≥25 kg/m^2	1.00 referent	0.96 (0.84, 1.10)	1.03 (0.90, 1.19)	1.05 (0.94, 1.16)	0.247
Total omega-6 (LA + AA)					
<25 kg/m^2	1.00 referent	1.07 (0.92, 1.22)	1.06 (0.93, 1.22)	1.10 (0.96, 1.26)	0.174
≥25 kg/m^2	1.00 referent	0.99 (0.89, 1.10)	1.07 (0.96, 1.18)	1.00 (0.90, 1.10)	0.765

Between study variability, measured by τ^2, ranged from 0 to 0.02 with a median of 0 and I^2 for heterogeneity ranged between 0 and 27% with a median of 0.
[a] Quartile cut-points for each individual study are given in Supplemental Table 1; sample sizes for BMI categories are: *n* = 14,012 (BMI < 25) and *n* = 18,669 (BMI ≥ 25).
[b] Adjusted for age, study, education, body mass index, race, smoking status, alcohol, menopausal status, age at menarche, age at first birth, parity, any use of hormone therapy, duration of oral contraceptive use, history of diabetes, history of hypertension, energy intake. All studies fit in one model by BMI group to improve model stability, rather than those with NCC indicators fit by conditional logistic regression and aggregated with others fit with logistic regression.
[c] Excludes the Southern Community Cohort Study and the Hormones and Diet in the Etiology of Breast Cancer Study due to small sample sizes for BMI subgroups.
[d] ORDET and the Netherlands Cohort Study on Diet and Cancer did not measure DPA; total long-chain omega-3 fatty acids are calculated as EPA + DHA for these studies.

endometrial cancer cases with rare histologies were excluded from the analysis. Associations were attenuated when quartiles were calculated across all studies (Supplemental Table 2).

In analyses stratified by body mass index (Table 3), moderate, 12–19% linear increases in endometrial cancer risk were observed for intakes of the individual LCn3PUFA, EPA, DPA, and DHA, as well as the summary measure (total LCn3PUFA, OR 1.16, 95% CI: 1.05–1.29; *P* trend<0.01) among heavier participants only (BMI ≥ 25 kg/m^2). No associations were observed among participants with BMI < 25 kg/m^2. Elevated risks for intakes of LCn3PUFA were only observed among White participants (total LCn3PUFA, OR 1.11; 95% CI: 1.02–1.21; *P* trend<0.01) (Table 4 and Supplemental Table 3), and no associations were observed for Black or Asian participants, though estimates were less precise because there were relatively few participants in these groups. Although associations were overall stronger for high-grade endometrial cancers (Table 5), point-estimates were inconsistent and variable across quartiles of intake and associations did not sustain log-linear trends.

Among the population-based case-control studies, risk for endometrial cancer associated with intakes of any fatty acid under study were around the null and there were no statistically significant trends with increasing intakes (Supplemental Table 6). For n6PUFA, when stratified by BMI (Supplemental Table 7), leaner participants had an elevated risk with greater intake of both LA and total n6PUFA with significant linear trends (*P* trend = 0.01 for each). For LCn3PUFA, none of the point estimates were significant, but a statistically significant trend of an increasing risk with increasing intake of EPA was noted in lean participants, but a decreasing risk with increasing intake among heavy participants.

4. Discussion

In this IPD meta-analysis of 12 prospective studies, we observed that dietary intakes of LCn3PUFA—DHA in particular—were associated with 5–10% elevated endometrial cancer risks overall, and 10–19% increases in risk among heavier participants.

Prior reports on the association between dietary LCn3PUFA and endometrial cancer risk are limited to the WHI [22], the Black Women's Health Study (BWHS) [23], a population-based case-control study in Connecticut [56]—each included in the present analysis—and the Vitamins And Lifestyle (VITAL) cohort study [21], which did not participate in E2C2. Among them, results have been inconsistent. Authors of the VITAL cohort reported 66–79% increased risks of endometrial cancer among participants who consumed the highest relative to the lowest energy-adjusted quintile of intake (EPA + DHA: Hazard Ratio [HR] 1.79, 95% CI: 1.16–2.75; *P* trend = 0.026) [21]. In contrast, a report from the WHI found that participants in the highest versus the lowest quintile of LCn3PUFA intake had 15%–23% reduced endometrial cancer incidence (EPA + DPA + DHA: HR 0.81, 95% CI: 0.66–1.00; *P* trend = 0.04) [22]. In the BWHS, intakes of dietary LCn3PUFA were not associated with endometrial cancer (EPA + DPA + DHA: HR 0.79, 95% CI:

Table 4
Individual-participant data meta-analysis of dietary polyunsaturated fatty acid intake in relation to endometrial cancer risk stratified by participants' race, *n* = 33,243.

	OR (95% CI)[a,b], Energy-adjusted study-specific quartiles				
Fatty acid (lipid number)	1	2	3	4	*P* trend
Omega-3					
α-linolenic acid (18:3n3; ALA)					
Asian/Pacific Islander	1.00 referent	0.97 (0.69, 1.38)	2.42 (0.81, 7.21)	0.97 (0.70, 1.33)	0.699
Black	1.00 referent	1.02 (0.77, 1.34)	0.95 (0.72.1.24)	0.91 (0.69, 1.18)	0.405
White	1.00 referent	1.05 (0.96, 1.15)	0.98 (0.90, 1.07)	0.99 (0.89, 1.09)	0.517
Eicosapentaenoic acid (20:5n3; EPA)					
Asian/Pacific Islander	1.00 referent	0.94 (0.60, 1.45)	1.11 (0.73, 1.69)	1.02 (0.60, 1.75)	0.944
Black	1.00 referent	1.08 (0.82, 1.43)	1.10 (0.84, 1.45)	0.97 (0.74, 1.27)	0.730
White	1.00 referent	0.98 (0.90, 1.07)	1.02 (0.94, 1.12)	1.08 (0.99, 1.17)	0.034
Docosapentaenoic acid (22:5n3; DPA)[b]					
Asian/Pacific Islander	1.00 referent	1.41 (0.41, 4.85)	0.94 (0.67, 1.32)	0.93 (0.67, 1.30)	0.757
Black	1.00 referent	1.19 (0.89, 1.60)	1.12 (0.84, 1.50)	1.06 (0.81, 1.38)	0.898
White	1.00 referent	0.97 (0.89, 1.07)	1.09 (1.00, 1.19)	1.10 (1.01, 1.20)	0.004
Docosahexaenoic acid (22:6n3; DHA)					
Asian/Pacific Islander	1.00 referent	0.83 (0.44, 1.57)	0.94 (0.52, 1.70)	1.03 (0.70, 1.52)	0.940
Black	1.00 referent	1.15 (0.87, 1.52)	1.12 (0.86, 1.48)	0.95 (0.72, 1.24)	0.545
White	1.00 referent	1.07 (0.98, 1.16)	1.07 (0.98, 1.17)	1.12 (1.03, 1.23)	0.004
Total long-chain omega-3 (EPA + DPA + DHA)[c]					
Asian/Pacific Islander	1.00 referent	0.72 (0.48, 1.07)	0.60 (0.27, 1.34)	0.89 (0.62, 1.27)	0.714
Black	1.00 referent	1.04 (0.78, 1.38)	1.07 (0.81, 1.40)	0.97 (0.74, 1.27)	0.783
White	1.00 referent	1.03 (0.95, 1.23)	1.07 (0.98, 1.16)	1.11 (1.02, 1.21)	0.007
Omega-6					
Linoleic acid (18:2n6; LA)					
Asian/Pacific Islander	1.00 referent	1.09 (0.60, 1.99)	1.21 (0.88, 1.67)	0.84 (0.60, 1.16)	0.624
Black	1.00 referent	1.61 (1.20, 2.16)	1.30 (0.98, 1.73)	1.12 (0.84, 1.48)	0.964
White	1.00 referent	1.01 (0.93, 1.10)	1.03 (0.95, 1.13)	1.04 (0.95, 1.13)	0.372
Arachidonic acid (20:4n6; AA)					
Asian/Pacific Islander	1.00 referent	0.82 (0.43, 1.56)	0.81 (0.41, 1.60)	0.88 (0.63, 1.23)	0.611
Black	1.00 referent	1.04 (0.76, 1.41)	1.00 (0.66, 1.51)	1.00 (0.76, 1.32)	0.982
White	1.00 referent	1.00 (0.90, 1.10)	1.05 (0.96, 1.14)	1.05 (0.96, 1.14)	0.253
Total omega-6 (LA + AA)					
Asian/Pacific Islander	1.00 referent	1.03 (0.58, 1.83)	1.19 (0.87, 1.63)	0.83 (0.60, 1.16)	0.626
Black	1.00 referent	1.61 (1.21, 2.16)	1.28 (0.96, 1.70)	1.12 (0.84, 1.48)	0.914
White	1.00 referent	1.00 (0.92, 1.09)	1.04 (0.95, 1.13)	1.04 (0.96, 1.13)	0.272

Between study variability, measured by τ^2, ranged from 0 to 0.66 with a median of 0 and I^2 for heterogeneity ranged between 0 and 58% with a median of 0.

[a] Quartile cut-points for each individual study are given in Supplemental Table 1; sample sizes for race categories are: n = 27,768 (White); *n* = 3177 (Black); and, *n* = 2005 (Asian/Pacific Islander).

[b] Adjusted for age, study, education, body mass index, and total energy. All studies fit in one model by race group to improve model stability, rather than those with NCC indicators fit by conditional logistic regression and aggregated with others fit with logistic regression.

[c] ORDET and the Netherlands Cohort Study on Diet and Cancer did not measure DPA; total long-chain omega-3 fatty acids are calculated as EPA + DHA for these studies.

Table 5
Individual-participant data meta-analysis of dietary polyunsaturated fatty acid intake in relation to endometrial cancer risk stratified by tumor grade, n = 33,243.

	OR (95% CI)[a,b], Energy-adjusted study-specific quartiles				
Fatty acid (lipid number)	1	2	3	4	*P* trend
Omega-3					
α-linolenic acid (18:3n3; ALA)					
Low-grade	1.00 referent	1.15 (1.04, 1.26)	1.07 (0.97, 1.17)	1.06 (0.96, 1.18)	0.451
High-grade	1.00 referent	0.82 (0.68, 0.99)	0.91 (0.78, 1.07)	0.93 (0.80, 1.09)	0.681
Eicosapentaenoic acid (20:5n3; EPA)					
Low-grade	1.00 referent	1.02 (0.93, 1.12)	1.07 (0.97, 1.18)	1.09 (0.97, 1.23)	0.117
High-grade	1.00 referent	1.08 (0.87, 1.33)	1.11 (0.87, 1.43)	1.09 (0.86, 1.39)	0.478
Docosapentaenoic acid (22:5n3; DPA)[c]					
Low-grade	1.00 referent	0.98 (0.89, 1.08)	1.11 (1.00, 1.22)	1.08 (0.98, 1.20)	0.040
High-grade	1.00 referent	1.12 (0.95, 1.33)	1.18 (0.95, 1.46)	1.14 (0.90, 1.45)	0.268
Docosahexaenoic acid (22:6n3; DHA)					
Low-grade	1.00 referent	1.05 (0.95, 1.15)	1.08 (0.98, 1.19)	1.11 (1.01, 1.22)	0.025
High-grade	1.00 referent	1.33 (1.13, 1.58)	1.28 (1.08, 1.51)	1.19 (1.00, 1.42)	0.148
Total long-chain omega-3 (EPA + DPA + DHA)[b]					
Low-grade	1.00 referent	1.01 (0.92, 1.11)	1.09 (0.97, 1.21)	1.09 (0.99, 1.19)	0.081
High-grade	1.00 referent	1.22 (1.03, 1.44)	1.16 (0.94, 1.44)	1.23 (0.98, 1.54)	0.175
Omega-6					
Linoleic acid (18:2n6; LA)					
Low-grade	1.00 referent	1.10 (0.96, 1.25)	1.09 (0.99, 1.20)	1.09 (0.99, 1.20)	0.099
High-grade	1.00 referent	0.96 (0.82, 1.13)	0.97 (0.82, 1.15)	0.95 (0.81, 1.12)	0.622
Arachidonic acid (20:4n6; AA)					
Low-grade	1.00 referent	1.01 (0.89, 1.14)	1.01 (0.89, 1.14)	1.01 (0.92, 1.12)	0.839
High-grade	1.00 referent	0.99 (0.84, 1.18)	1.12 (0.95, 1.32)	0.98 (0.78, 1.22)	0.656
Total omega-6 (LA + AA)					
Low-grade	1.00 referent	1.08 (0.97, 1.20)	1.09 (0.99, 1.20)	1.09 (0.99, 1.20)	0.078
High-grade	1.00 referent	0.93 (0.79, 1.10)	0.99 (0.84, 1.17)	0.94 (0.80, 1.11)	0.694

Between study variability, measured by τ^2, ranged from 0 to 0.05 with a median of 0 and I^2 for heterogeneity ranged between 0 and 442% with a median of 0.

[a] Quartile cut-points for each individual study are given in Supplemental Table 1; sample sizes for cancer pathologic groupings are: n = 4595 (low-grade endometrial cancer cases); n = 1322 (high-grade endometrial cancer cases); and, n = 26,031 (controls).

[b] Adjusted for age, study, body mass index, smoking status, energy intake. All studies fit in one model by grade group to improve model stability, rather than those with NCC indicators fit by conditional logistic regression and aggregated with others fit with logistic regression.

[c] ORDET and the Netherlands Cohort Study on Diet and Cancer did not measure DPA; total long-chain omega-3 fatty acids are calculated as EPA + DHA for these studies.

0.51–1.24; *P* trend = 0.605) [23], while the authors from the Connecticut case-control study observed strong inverse associations for dietary intakes of EPA (Q4 vs. Q1: OR 0.57, 95% CI: 0.39–0.84) and DHA (OR 0.64, 95% CI: 0.44–0.94) [56]. The mean energy-adjusted daily intakes of total LCn3PUFA were generally similar across prior studies: 193 mg/d in VITAL, 143 mg/d in WHI, 121 & 196 mg/d in the BWHS (measured at two time points) [23], and 219 mg/d in the Connecticut case-control study (given in Supplemental Table 5). The mean daily intake in the present analysis was comparable at 161 mg/d, although differences were observed across participating studies and the upper quartile cut-points varied from ≥101 to ≥477 mg/d (Supplemental Table 1).

Although not directly comparable to the present study, there is additional evidence of elevated associations between LCn3PUFA and cancer risk. Studies of dietary fish consumption, from which LCn3PUFA are derived, have been suggestive of elevated endometrial cancer risks [57,58]. Further, results from a large-scale randomized, placebo-controlled prevention trial of fish oil (1 g/day) supplementation versus a placebo were suggestive of elevated risk of invasive cancer among a subgroup of participants who consumed ≥1.5 servings/week of fish (HR 1.13, 95% CI: 0.98–1.31) [59]. Similarly, results from the UK Biobank prospective cohort study of over 250,000 largely European participants were also suggestive that fish oil supplementation was associated with small elevations in endometrial cancer risk (HR 1.09, 95% CI: 0.93–1.28), which were strengthened among participants who consumed fatty fish ≥2/week (HR 1.24, 95% CI: 0.89–1.72) [60].

We observed 12–19% elevated associations between LCn3PUFA intake and endometrial cancer risk restricted to overweight/obese participants (BMI ≥ 25 kg/m^2), and no association among leaner participants. In contrast, prior studies observed inverse [21,22] or suggestive [23] 41–61% inverse associations between the upper versus the lower quintile of LCn3PUFA intakes and endometrial cancer risk among leaner participants (BMI < 25 kg/m^2). Nevertheless, our findings are consistent in direction—but not in magnitude—with those reported from the VITAL cohort [21], where total dietary LCn3PUFA intake was associated with nearly three-fold increases in endometrial cancer risk among participants with BMI ≥ 25 kg/m^2 (HR 2.75, 95% CI: 1.62–4.68).

We lastly observed no clear differences in the association of LCn3PUFA by race or with endometrial cancer grade. Only the prior report from the BWHS (included in the present analysis) has examined associations of dietary LCn3PUFA with endometrial cancer risk among non-White participants [23]. The BWHS, Multiethnic Cohort, NIH-AARP Diet and Health Study, and the WHI, contributed the vast majority of Black or Asian participants to the present analysis (Supplemental Table 3). Only the prior report from the WHI had sufficient sample size to examine associations by endometrial cancer pathologic grouping, which were defined in a similar manner as the present study [22]. In that study, LCn3PUFA intakes were inversely associated with low-grade and not clearly associated with high-grade endometrial cancers [22]. Similar to the present study which includes WHI data, HRs for high-grade endometrial cancers were above 1.0 and ranged between 1.08 and 1.63 [22].

LCn3PUFA have been shown to hold anti-inflammatory properties in observational epidemiologic studies [14,15], and randomized clinical trials [16–18]. In human trials, LCn3PUFA supplementation reduced several blood biomarkers of inflammation including C-reactive protein [16,18], tumor necrosis factor-α [18], and IL-2 [17]. LCn3PUFA are further hypothesized to hold chemopreventive properties for endometrial cancer as inhibition of the COX-2 blockage is associated with reductions in estrogen synthesis [20,61], which is an important catalyst of endometrial proliferation [62,63]. There are few clear biological mechanisms that may explain the observed elevations in risk overall or among heavier participants. It is possible that inhibition of IL-2 may inhibit cytotoxic T-cell differentiation, thereby promoting tumor immune evasion [64,65]. Another hypothesis is that lipophilic persistent organic pollutants such as heavy metals or organochlorines may explain these associations, however epidemiologic evidence of an association is limited [66–71]. Although it is plausible that

women who consume fatty fish may be healthier and therefore practice other healthy behaviors, such as seeing their physician, detection bias is an unlikely explanation for our findings as there is no population-based screening for endometrial cancer.

This study has several strengths. With only three prior prospective cohort studies having reported on this association, this IPD meta-analysis of 12 studies (with two overlapping) adds considerable new evidence to this area of research. This study has by far the largest number of cases and is sufficiently powered to examine the association between estimated dietary intakes of LCn3PUFA and endometrial cancer risk, as well as to examine these associations within subgroups characterized by race, body size, and cancer histology. This report is further strengthened by comprehensive measurement of and adjustment for endometrial cancer risk factors.

Our results should nevertheless be considered in the context of their limitations. Some endometrial cancer risk factors were unavailable for adjustment (e.g., family history of endometrial cancer, history of estrogen-only hormone therapy) across all studies, and others were incompletely adjusted for because of harmonization procedures. Therefore, it remains possible that residual confounding from a single factor or combination of factors may explain our findings. This study heavily relied on data derived from several different FFQs that are subject to reporting and measurement errors and biases [72]; however, given the prospective nature of the participating studies, statistically significant associations observed here may be despite these limitations. Error in the estimation of energy intake may have resulted in residual (negative) confounding, again resulting in underestimations of the associations. With eight fatty acids/fatty acid groupings under study categorized into quartiles, there is potential for Type I error inflation. Additionally, the nested case-control sets for sampling were only available for two studies, which has the potential to underestimate standard errors resulting in inadvertently narrow 95% CI. We were also unable to examine the association between LCn3PUFA from dietary supplementation (i.e., fish oil) and endometrial cancer; this non-differential measurement error in prospective studies would serve to attenuate associations and may suggest that a true association is stronger than we report. Our ability to control for potential confounding in race-stratified regression models was limited due to the relatively small numbers of Asian and Black participants within the individual studies. Further, due to missingness we were unable to further characterize participants by Hispanic ethnicity.

Higher dietary intakes of LCn3PUFA are unlikely to reduce endometrial cancer incidence, rather they may be associated with small to moderate elevated risks in some subgroups of women. The United States Department of Health and Human Services and Department of Agriculture advise women to consume two servings of fish per week [73], more so (depending upon the type of fish) if pregnant or breastfeeding [74]. Well-powered randomized clinical trials are needed to confirm these findings, especially among high-risk women. If our results are confirmed, clinicians should consider their patients' diets and weigh the risks and benefits of adherence to such recommendations when assessing their patients' risk of endometrial cancer, and when offering advice aimed at lowering their risk.

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Data Availability

No new data were generated or analyzed in support of this research. The data underlying this article cannot be shared publicly due to constraints of existing participant consent documentation.

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Black Women's Health Study: Data on endometrial cancer pathology were obtained from several state cancer registries (AZ, CA, CO, CT, DE, DC, FL, GA, IL, IN, KY, LA, MD, MA, MI, NJ, NY, NC, OK, PA, SC, TN, TX, VA). The BWHS study protocol was approved by the Boston University Medical Campus Institutional Review Board (IRB) and by the IRBs of participating cancer registries as required. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute, the National Institutes of Health, or the state cancer registries. We thank participants and staff of the BWHS for their contributions.

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Novelty & Impact

Limited data from prospective studies suggest inverse associations between intakes of long-chain omega-3 fatty acids and endometrial cancer risk. Utilizing consortium data, we performed an individual-participant data meta-analysis to comprehensively examine these associations overall and in subgroups. We found that higher dietary intakes of long-chain omega-3 fatty acids are unlikely to reduce endometrial cancer incidence; rather, they may be associated with small to moderate increases in risk in some subgroups of women, particularly overweight/obese women.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.10.015.

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