Long-chain ω-3 fatty acid intake and endometrial cancer risk in the Women's Health Initiative[1–5]

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ABSTRACT

Background: Inflammation may be important in endometrial cancer development. Long-chain ω-3 (n–3) polyunsaturated fatty acids (LCω-3PUFAs) may reduce inflammation and, therefore, reduce cancer risk. Because body mass is associated with both inflammation and endometrial cancer risk, it may modify the association of fat intake on risk.

Objective: We examined whether intakes of LCω-3PUFAs were associated with endometrial cancer risk overall and stratified by body size and histologic subtype.

Design: Women were n = 87,360 participants of the Women's Health Initiative Observational Study and Clinical Trials who were aged 50–79 y, had an intact uterus, and completed a baseline food-frequency questionnaire. After 13 y of follow-up, n = 1253 incident invasive endometrial cancers were identified. Cox regression models were used to estimate HRs and 95% CIs for the association of intakes of individual ω-3 fatty acids and fish with endometrial cancer risk.

Results: Intakes of individual LCω-3PUFAs were associated with 15–23% linear reductions in endometrial cancer risk. In women with body mass index (BMI; in kg/m^2) <25, those in the upper compared with lowest quintiles of total LCω-3PUFA intake (sum of eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids) had significantly reduced endometrial cancer risk (HR: 0.59; 95% CI: 0.40, 0.82; P-trend = 0.001), whereas there was little evidence of an association in overweight or obese women. The reduction in risk observed in normal-weight women was further specific to type I cancers.

Conclusions: Long-chain ω-3 intake was associated with reduced endometrial cancer risk only in normal-weight women. Additional studies that use biomarkers of ω-3 intake are needed to more accurately estimate their effects on endometrial cancer risk. This trial was registered at clinicaltrials.gov as NCT00000611. *Am J Clin Nutr* 2015;101:824–34.

Keywords: eicosapentaenoic acid, endometrial cancer, docosahexaenoic acid, fish, omega-3

INTRODUCTION

Inflammation plays an important role in the cause of endometrial cancer (1, 2). Prospective studies showed that increases in circulating biomarkers of inflammation are associated with increases in endometrial cancer risk (3–5), and the use of nonsteroidal anti-inflammatory drugs may decrease risk (6). However, relatively little is known regarding how other modifiable lifestyle factors with anti-inflammatory properties may affect endometrial cancer risk.

Intakes of long-chain ω-3 PUFAs (LCω-3PUFAs),[6] which derive primarily from consumption of fatty fish and fish-oil supplements, were associated with reduced inflammation in observational studies (7, 8) and randomized clinical trials (CTs) (9–11). The anti-inflammatory properties of LCω-3PUFAs are thought to be due primarily to the inhibition of nuclear factor κB and downstream modulation of the cyclooxygenase-2 pathway (12). LCω-3PUFAs have further been hypothesized to have chemoprotective properties for endometrial cancers because the inhibition of the cyclooxygenase-2 blockade is associated with

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[4] Supplemental Tables 1 and 2 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[6] Abbreviations used: AA, arachidonic acid; ALA, α-linolenic acid; CT, clinical trial; DPA, docosapentaenoic acid; FFQ, food-frequency questionnaire; LCω-3PUFA, long-chain ω-3 PUFA; OS, observational study; VITAL, Vitamins and Lifestyle; WHI, Women's Health Initiative.

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TABLE 1
Distributions of WHI participants' characteristics by total long-chain ω-3 fatty acids (n = 87,360)[1]

	Energy-adjusted quintiles of total long-chain ω-3 PUFAs (mg/d)					
Demographics and anthropometric measures	≤56.8 (n = 17,472)	56.9–91.2 (n = 17,472)	91.3–133.9 (n = 17,472)	134.0–205.2 (n = 17,472)	>205.2 (n = 17,472)	P
Age,[2] y	62.7 ± 7.3	63.3 ± 7.3	63.1 ± 7.2	62.9 ± 7.1	62.8 ± 7.0	0.175
Race, n (%)						<0.001
White	15,428 (88.3)	15,067 (86.2)	14,914 (85.4)	14,836 (84.9)	14,205 (81.3)	
Black	707 (4.0)	1058 (6.1)	1215 (7.0)	1270 (7.3)	1495 (8.6)	
Hispanic	858 (4.9)	757 (4.3)	634 (3.6)	473 (2.7)	443 (2.5)	
Asian/Pacific Islander	177 (1.0)	290 (1.7)	443 (2.5)	610 (3.5)	1009 (5.8)	
Other race	302 (1.7)	300 (1.7)	266 (1.5)	283 (1.6)	320 (1.8)	
Education, n (%)						<0.001
≤High school graduate	4393 (25.3)	4282 (24.7)	3664 (21.1)	2884 (16.6)	2260 (13.0)	
Some college	6422 (37.0)	6593 (38.0)	6391 (36.8)	5944 (34.3)	5486 (31.7)	
College or advanced degree	6548 (37.7)	6480 (37.3)	7301 (42.1)	8524 (49.1)	9575 (55.3)	
WHI enrollment, n (%)						<0.001
Observational study	8403 (48.1)	7916 (45.3)	7747 (44.3)	7498 (42.9)	6893 (39.5)	
Clinical trials	9069 (51.9)	9556 (54.7)	9725 (55.7)	9974 (57.1)	10,579 (60.5)	
Lifestyle characteristics, n (%)						
BMI (kg/m^2)						<0.001
<25.0	6265 (36.2)	6567 (37.9)	6574 (38.0)	6700 (38.7)	6758 (39.0)	
25.0–29.9	5826 (33.6)	5945 (34.3)	5993 (34.6)	5972 (34.5)	5877 (33.9)	
30.0–34.9	3202 (18.5)	3063 (17.7)	2990 (17.3)	2864 (16.6)	2859 (16.5)	
≥35.0	2024 (11.7)	1757 (10.1)	1759 (10.2)	1765 (10.2)	1818 (10.5)	
Physical activity						<0.001
Inactive	3198 (19.4)	2865 (17.2)	2351 (14.1)	2046 (12.2)	1735 (10.3)	
>0–7.2 MET-h/wk	5023 (30.4)	5087 (30.6)	4963 (29.8)	4489 (26.8)	4072 (24.1)	
7.3–17.2 MET-h/wk	4292 (26.0)	4653 (28.0)	4723 (28.3)	5084 (30.4)	5000 (29.6)	
≥17.3 MET-h/wk	4014 (24.3)	4042 (24.3)	4630 (27.8)	5119 (30.6)	6070 (36.0)	
Smoking						<0.001
Never smoker	9156 (54.0)	9112 (53.9)	8628 (51.2)	8487 (50.5)	8081 (48.2)	
>0–7.4 pack-years	2469 (14.6)	2501 (14.8)	2743 (16.3)	2781 (16.5)	2910 (17.4)	
7.5–23.0 pack-years	2380 (14.0)	2440 (14.4)	2594 (15.4)	2703 (16.1)	2879 (17.2)	
≥23.1 pack-years	2953 (17.4)	2856 (16.9)	2895 (17.2)	2849 (16.9)	2896 (17.3)	
Alcohol (servings/wk)						<0.001
0	8495 (48.6)	7733 (44.3)	6641 (38.0)	5737 (32.9)	5334 (30.6)	
>0–0.9	3356 (19.2)	3685 (21.1)	3708 (21.2)	3656 (20.9)	3373 (19.3)	
1.0–4.0	2927 (16.8)	3137 (18.0)	3698 (21.2)	3962 (22.7)	4068 (23.3)	
≥4.1	2684 (15.4)	2897 (16.6)	3408 (19.5)	4105 (23.5)	4675 (26.8)	
Medical history and reproductive health, n (%)						
Family history of endometrial cancer						0.012
No	15,460 (94.7)	15,420 (94.4)	15,450 (94.3)	15,533 (94.8)	15,549 (95.1)	
Yes	868 (5.3)	907 (5.6)	936 (5.7)	850 (5.2)	802 (4.9)	
Age at menarche (y)						<0.001
≤10	975 (5.6)	961 (5.5)	995 (5.7)	1102 (6.3)	1170 (6.7)	
11–12	6964 (40.0)	6999 (40.2)	7090 (40.7)	7098 (40.7)	7268 (41.7)	
13–14	7732 (44.4)	7621 (43.7)	7657 (43.9)	7570 (43.5)	7390 (42.4)	
≥15	1753 (10.1)	1845 (10.6)	1693 (9.7)	1650 (9.5)	1603 (9.2)	
Age at menopause (y)						<0.001
<47	3236 (19.6)	3164 (19.1)	3054 (18.3)	2803 (16.8)	2622 (15.6)	
47–51	6905 (41.9)	6917 (41.8)	6865 (41.1)	6836 (41.0)	6859 (40.9)	
≥52	6353 (38.5)	6469 (39.1)	6766 (40.6)	7053 (42.3)	7274 (43.4)	
Parity						<0.001
Nulliparous or nulligravida	2156 (12.4)	2156 (12.4)	2162 (12.4)	2236 (12.9)	2456 (14.1)	
1	1525 (8.8)	1448 (8.3)	1543 (8.9)	1531 (8.8)	1574 (9.1)	
2–4	10,935 (62.9)	11,022 (63.3)	11,154 (64.1)	11,269 (64.8)	11,463 (66.0)	
≥5	2780 (16.0)	2778 (16.0)	2548 (14.6)	2346 (13.5)	1887 (10.9)	
Age at first birth						<0.001
Nulliparous or nulligravida	2156 (13.5)	2156 (13.6)	2162 (13.6)	2236 (14.1)	2456 (15.5)	
<20 y	2008 (12.6)	1937 (12.2)	1756 (11.1)	1474 (9.3)	1348 (8.5)	
20–29 y	10,263 (64.3)	10,258 (64.8)	10,428 (65.7)	10,620 (66.8)	10,437 (65.9)	
≥30 y	1543 (9.7)	1472 (9.3)	1523 (9.6)	1571 (9.9)	1608 (10.1)	

(Continued)

TABLE 1 (*Continued*)

Demographics and anthropometric measures	Energy-adjusted quintiles of total long-chain ω-3 PUFAs (mg/d)					*P*
	≤56.8 (*n* = 17,472)	56.9–91.2 (*n* = 17,472)	91.3–133.9 (*n* = 17,472)	134.0–205.2 (*n* = 17,472)	>205.2 (*n* = 17,472)	
Duration of combined hormone therapy (y)						<0.001
<2.5	12,346 (70.7)	12,387 (70.9)	12,000 (68.7)	11,831 (67.7)	11,850 (67.8)	
2.5–7	2632 (15.1)	2551 (14.6)	2697 (15.4)	2776 (15.9)	2824 (16.2)	
≥8	2494 (14.3)	2534 (14.5)	2774 (15.9)	2864 (16.4)	2798 (16.0)	
Duration of unopposed estrogen therapy (y)						0.032
<2.5	16,445 (94.1)	16,411 (93.9)	16,444 (94.1)	16,483 (94.3)	16,557 (94.8)	
2.5–7	587 (3.4)	584 (3.3)	559 (3.2)	526 (3.0)	511 (2.9)	
≥8	440 (2.5)	477 (2.7)	469 (2.7)	462 (2.6)	404 (2.3)	
Duration of oral contraceptive use (y)						0.004
≤4	14,066 (80.5)	14,132 (80.9)	14,008 (80.2)	13,842 (79.3)	13,907 (79.6)	
5–12	2632 (15.1)	2531 (14.5)	2631 (15.1)	2746 (15.7)	2689 (15.4)	
>12	771 (4.4)	807 (4.6)	826 (4.7)	874 (5.0)	872 (5.0)	
Oophorectomy status						0.139
No	16,615 (95.5)	16,592 (95.2)	16,641 (95.6)	16,599 (95.4)	16,546 (95.1)	
Yes	786 (4.5)	830 (4.8)	762 (4.4)	798 (4.6)	855 (4.9)	
History of diabetes						0.007
No	16,684 (95.5)	16,571 (94.9)	16,571 (94.9)	16,615 (95.1)	16,552 (94.8)	
Yes	778 (4.5)	890 (5.1)	895 (5.1)	850 (4.9)	913 (5.2)	

[1]Sum of EPA (20:5ω-3), docosapentaenoic acid (22:5ω-3), and DHA (22:6ω-3). *P* value for age was derived from the *F* test; all other comparisons were derived from chi-square tests of independence. MET-h, metabolic equivalent task hours; WHI, Women's Health Initiative.

[2]All values are means ± SDs.

reductions in estrogen synthesis (13, 14), which is a major driver of endometrial proliferation (15, 16).

In the only prospective study, to our knowledge, to examine the association between dietary LCω-3PUFA intake and endometrial cancer risk, we recently reported that high dietary intakes of LCω-3PUFAs were associated with 66–79% increases in endometrial cancer risk in 24,494 women in the Vitamins and Lifestyle (VITAL) cohort study (*n* cases = 263) (17); however, increases in risk were only observed in overweight women, whereas strong, linear reductions in risk were observed in normal-weight women.

In an attempt to verify these findings, we examined associations of dietary LCω-3PUFAs and their fish sources with endometrial cancer risk overall and stratified by BMI (in kg/m^2) in participants of the WHI (Women's Health Initiative), which is a much-larger cohort of postmenopausal women with longer follow-up. Because of recommendations by the American Heart Association to eat ≥2 servings fatty fish/wk for cardiovascular disease prevention (18), despite waning evidence of a benefit (19), findings from this analysis should help further inform women of their potential risks and benefits with regard to the single most-common gynecologic malignancy in the United States.

METHODS

WHI

The WHI was a large, prospective study of 161,808 postmenopausal women that was designed to examine common causes of morbidity and mortality in postmenopausal women, including cancer, cardiovascular disease, and osteoporosis (20). The study consists of a multifactorial CT (clinicaltrials.gov: NCT00000611) and an observational study (OS). WHI methods are detailed elsewhere (20–22). Women, aged 50–79 y, were recruited at 40 US clinical centers between 1 September 1993 and 31 December1998. The WHI CT included 3 overlapping components as follows: 2 placebo-controlled hormone therapy trials (estrogen alone: *n* = 10,739; estrogen plus progestin: *n* = 16,608), a dietary modification trial (*n* = 48,835), and a calcium and vitamin D–supplementation placebo-controlled trial (*n* = 36,282) (23–25). Women who were screened for participation in the CT but were ineligible or unwilling to participate were offered participation in the OS (*n* = 93,676) (26). After the original study ended in 2005, the WHI Extension Study (2005–2010) was carried out to collect an additional 5 y of follow-up data. Women provided written informed consent for participation in both the original and extension studies. Human subject review committees at all participating institutions approved the WHI study protocol.

In the current analysis, exclusions were made for women who reported at baseline a positive history of breast, ovarian, or uterine/endometrial cancer or were missing these data (*n* = 10,457), had a hysterectomy at baseline or hysterectomy status was unknown (*n* = 67,789), and did not complete a baseline food-frequency questionnaire (FFQ; *n* = 4892). After these exclusions, there were *n* = 87,360 women available for study.

Data collection

WHI participants attended baseline screening visits during which they completed self-administered questionnaires that collected detailed information on demographics, medical and reproductive histories, family history of cancer, physical activity, and other risk factors. Height and weight were measured by clinic staff and used to compute BMI. Although women were asked about dietary supplement use, they were not asked specifically about fish oil.

Women also completed at baseline a semiquantitative FFQ (27). Participants reported their usual frequencies and portion sizes (small, medium, or large relative to the stated medium portion size and photographs of portion sizes) of 122 foods and beverages consumed during the 3 mo before baseline. The questionnaire was designed specifically to improve the measurement of fat intake by including questions about food preparation and types of fats added in cooking or at the table. The average daily intake of specific fatty acids was calculated by multiplying the adjusted serving size of each specific food by its fatty acid content as determined by the University of Minnesota's Nutrient Data System for Research (28). Women were queried on their intakes of baked/broiled white fish (examples include halibut and cod); dark or oily fish (e.g., salmon and fresh tuna); shellfish (e.g., shrimp and lobster); canned tuna, tuna salad, or tuna casserole; and fried fish/shellfish. A summary variable baked/broiled fish, which represented the sum of all intakes except fried fish/shellfish was created. Summary variables that represented total LCω-3PUFAs [expressed as mg/d; defined in the current study as EPA (20:5ω-3) plus docosapentaenoic acid (DPA; 22:5ω-3) plus DHA (22:6ω-3)] and total ω-6 (defined as linoleic acid (18:2ω-6) plus arachidonic acid (AA; 20:4ω-6) were also created. Fish data were categorized into no intake (0 servings/wk) and quartiles of intake. Fatty acids were energy-adjusted by using the residual method (29) as follows: *1*) fatty acid intakes were regressed on energy intake and *2*) mean fatty acid intake was added to the residual of the regression and *3*) categorized into quintiles. Therefore, quintile ranges are given in tables as energy-adjusted milligrams per day of intake. The majority of EPA, DPA, and DHA consumed came from fish intake with the largest contributions from dark fish and minor amounts contributed through the consumption of poultry and lunch meats.

Follow-up for cancer and censoring

Incident, invasive endometrial cancers were reported by a questionnaire semi-annually in the CT during the main WHI trial and annually thereafter and annually in the OS. Medical records were obtained and reviewed, and diagnoses were confirmed, by physician adjudicators. After a median follow-up of 13.0 y, $n = 1253$ invasive endometrial cancers were identified. Aside from a cancer diagnosis, participants were right censored from the analysis at the earliest date of the following occurrences: end of original follow-up for participants who were not enrolled in WHI Extension studies, withdrawal from the study, death, incident endometrial carcinoma in situ, incident uterine cancer of mesenchymal origin, postbaseline hysterectomy, loss of contact, or 17 September 2010, which was the last date of the WHI Extension Study data adjudication. Type I cancers ($n = 1032$) were predominantly adenocarcinoma, not otherwise specified, or endometrioid adenocarcinoma. Type II cancers ($n = 180$) included papillary, clear cell, and serous adenocarcinomas as well as carcinosarcomas. Analyses stratified by histologic subtype were censored at their respective times at diagnosis for $n = 40$ cancers that were not readily classified as types I or II (including mucinous adenocarcinomas, endometrial stromal sarcomas, and small cell or squamous cell carcinomas).

Statistical analyses

Cox proportional hazards models that used baseline age as the time variable were used to estimate age and energy-adjusted and multivariable-adjusted HRs and 95% CIs for associations between fatty acid or fish intake and endometrial cancer risk. We selected a priori known or suspected risk factors for endometrial cancer for inclusion in regression models. Cox models were adjusted for the following variables: age (time variable), US region, race, education, BMI, smoking pack-years, alcohol consumption, physical activity (metabolic-equivalent task hours per week), age at menarche, age at first birth, age as menopause, parity, duration of combined hormone therapy, duration of estrogen-only hormone therapy, duration of oral contraceptive use, oophorectomy status, family history of endometrial cancer, history of diabetes, and energy intake (in kcal). *P*-trend values were calculated across categories of exposure by treating ordinal categorical fatty acid or fish variables as continuous in Cox models. *P*-values for the difference in associations between fatty acids and endometrial cancer subtypes (*P*-difference) (i.e., type I compared with type II) were compared by using a case-only–adjusted logistic regression model. All reported *P* values were 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SAS v9.3 software (SAS Institute Inc.).

In addition, we examined the effect modification of associations between LCω-3PUFA or fish intake and endometrial cancer

TABLE 2
Correlations between dietary PUFAs in the WHI Observational Study and Clinical Trials ($n = 87{,}360$)[1]

	Energy-adjusted dietary PUFAs (mg/d)							
	EPA (20:5ω-3)	DPA (22:5ω-3)	DHA (22:6ω-3)	EPA + DPA + DHA	ALA (18:3ω-3)	LA (18:2ω-6)	AA (20:4ω-6)	LA + AA
EPA (20:5ω-3)	1.00							
DPA (22:5ω-3)	0.85	1.00						
DHA (22:6ω-3)	0.93	0.87	1.00					
EPA + DPA + DHA	0.97	0.90	0.99	1.00				
ALA (18:3ω-3)	0.05	0.01	0.05	0.05	1.00			
LA (18:2ω-6)	−0.05	−0.06	−0.05	−0.05	0.11	1.00		
AA (20:4ω-6)	0.42	0.60	0.49	0.49	0.73	0.13	1.00	
LA + AA	−0.05	−0.05	−0.04	−0.05	0.73	1.00	0.15	1.00

[1]Spearman rank correlation coefficients of energy-adjusted dietary intakes; *P*-all such comparisons < 0.001. AA, arachidonic acid; ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid; WHI, Women's Health Initiative.

risk by stratifying results by BMI (<25 compared with ≥25) with additional adjustment for continuous BMI within these strata. This method was undertaken for the following 2 reasons: *1*) BMI is strongly correlated with inflammation (30) and postmenopausal estrogen signaling (31), and *2*) we reported large differences in associations by BMI in our previous report (17). We grouped overweight (BMI ≥25 to <30) and obese women (BMI ≥) in the current study because HRs for these categories were similar. *P*-interaction values were calculated by using the likelihood ratio test for the inclusion of a crossproduct term of the ordinal categorical exposure and 2-category effect-modifier.

RESULTS

Distributions of WHI participants' characteristics by total LCω-3PUFA intake are given in **Table 1**. Women who consumed the highest compared with lowest amounts of LCω-3PUFAs tended to be black or Asian, be educated, have lower BMI, and were more physically active. In addition, they smoked, drank more alcohol, had earlier ages at menarche, later ages at menopause, fewer children, and used combined postmenopausal hormones or oral contraceptives longer.

Correlations between dietary intakes of individual PUFAs are given in **Table 2**. Intakes of LCω-3PUFAs EPA, DPA, and DHA

TABLE 3
Association between dietary ω-3 PUFA intake and endometrial cancer risk in the WHI Observational Study and Clinical Trials (n = 87,360)[1]

	Energy-adjusted quintiles of fatty acid intake					
	1	2	3	4	5	*P*-trend
ω-3 Fatty acids						
EPA + DPA + DHA, mg/d	≤56.8	56.9–91.2	91.3–133.9	134.0–205.2	>205.2	
Cases, *n*	267	238	271	241	236	
HR (95% CI)[2]	1.00 (reference)	0.96 (0.81, 1.15)	1.09 (0.92, 1.30)	0.95 (0.80, 1.14)	0.92 (0.77, 1.09)	0.353
HR (95% CI)[3]	1.00 (reference)	0.98 (0.80, 1.20)	1.03 (0.84, 1.26)	0.90 (0.73, 1.11)	0.81 (0.66, 1.00)	0.040
EPA (20:5ω-3), mg/d	≤15.6	15.7–27.4	27.5–41.3	41.4–63.6	>63.6	
Cases, *n*	262	253	244	266	228	
HR (95% CI)[2]	1.00 (reference)	1.05 (0.88, 1.25)	1.00 (0.84, 1.20)	1.08 (0.91, 1.28)	0.91 (0.76, 1.08)	0.427
HR (95% CI)[3]	1.00 (reference)	1.09 (0.89, 1.33)	0.96 (0.78, 1.18)	1.00 (0.81, 1.22)	0.81 (0.65, 1.01)	0.043
DPA (22:5ω-3), mg/d	≤6.8	6.9–10.7	10.8–15.2	15.3–22.2	>22.2	
Cases, *n*	271	252	248	242	240	
HR (95% CI)[2]	1.00 (reference)	1.00 (0.84, 1.19)	0.98 (0.82, 1.17)	0.94 (0.79, 1.12)	0.92 (0.77, 1.09)	0.239
HR (95% CI)[3]	1.00 (reference)	1.03 (0.84, 1.26)	0.95 (0.78, 1.17)	0.81 (0.66, 1.00)	0.85 (0.69, 1.05)	0.019
DHA (22:6ω-3), mg/d	≤32.8	32.9–51.9	52.0–76.8	76.9–121.0	>121.0	
Cases, *n*	283	232	263	236	239	
HR (95% CI)[2]	1.00 (reference)	0.89 (0.74, 1.06)	1.00 (0.84, 1.19)	0.88 (0.74, 1.05)	0.87 (0.74, 1.04)	0.157
HR (95% CI)[3]	1.00 (reference)	0.91 (0.74, 1.11)	0.97 (0.79, 1.18)	0.81 (0.66, 1.00)	0.77 (0.63, 0.95)	0.010
ALA (18:3ω-3), mg/d	≤921.6	921.7–1130.6	1130.7–1333.1	1333.2–1640.0	>1640.0	
Cases, *n*	285	244	221	241	236	
HR (95% CI)[2]	1.00 (reference)	0.93 (0.78, 1.11)	0.85 (0.71, 1.02)	0.92 (0.77, 1.09)	0.96 (0.81, 1.13)	0.604
HR (95% CI)[3]	1.00 (reference)	0.94 (0.77, 1.15)	0.83 (0.67, 1.02)	0.98 (0.80, 1.21)	0.96 (0.79, 1.18)	0.900
ω-6 Fatty acids						
LA + AA, mg/d	≤8328.5	8328.6–10,061.7	10,061.8–11,539.7	11,539.8–13,494.5	>13,494.5	
Cases, *n*	270	234	229	242	278	
HR (95% CI)[2]	1.00 (reference)	0.93 (0.78, 1.12)	0.93 (0.78, 1.12)	0.98 (0.82, 1.18)	1.08 (0.91, 1.27)	0.296
HR (95% CI)[3]	1.00 (reference)	0.81 (0.66, 1.00)	0.88 (0.72, 1.09)	0.94 (0.76, 1.17)	1.09 (0.89, 1.34)	0.180
LA (18:2ω-6), mg/d	≤8235.9	8236.0–9962.1	9962.2–11,438.1	11,438.2–13,391.3	>13,391.3	
Cases, *n*	270	234	230	242	277	
HR (95% CI)[2]	1.00 (reference)	0.93 (0.78, 1.12)	0.94 (0.78, 1.12)	0.99 (0.83, 1.18)	1.07 (0.91, 1.27)	0.315
HR (95% CI)[3]	1.00 (reference)	0.79 (0.64, 0.98)	0.88 (0.71, 1.08)	0.93 (0.76, 1.15)	1.08 (0.88, 1.32)	0.216
AA (20:4ω-6), mg/d	≤61.5	61.6–80.9	81.0–99.8	99.9–127.5	>127.5	
Cases, *n*	304	238	229	225	257	
HR (95% CI)[2]	1.00 (reference)	0.84 (0.70, 0.99)	0.81 (0.68, 0.97)	0.80 (0.67, 0.95)	0.90 (0.76, 1.06)	0.163
HR (95% CI)[3]	1.00 (reference)	0.78 (0.64, 0.95)	0.77 (0.63, 0.94)	0.71 (0.58, 0.87)	0.75 (0.61, 0.91)	0.002
ω-3:ω-6						
Ratio of EPA + DPA + DHA to LA + AA, mg/d	≤0.005	0.006–0.008	0.009–0.013	0.014–0.021	>0.021	
Cases, *n*	269	248	241	259	236	
HR (95% CI)[2]	1.00 (reference)	1.01 (0.84, 1.20)	0.97 (0.81, 1.15)	1.02 (0.85, 1.21)	0.90 (0.75, 1.07)	0.292
HR (95% CI)[3]	1.00 (reference)	0.99 (0.80, 1.21)	0.92 (0.75, 1.13)	0.94 (0.76, 1.15)	0.81 (0.65, 1.00)	0.053

[1] *P*-trend values were calculated by treating categorical exposure variables as continuous in regression models. AA, arachidonic acid; ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid; WHI, Women's Health Initiative.

[2] Derived from Cox proportional hazards regression models adjusted for age (time variable) and total energy.

[3] Further adjusted for clinical trial/observational study 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.

were strongly and positively correlated ($r > 0.85$), whereas each was slightly and inversely correlated ($r \leq -0.05$) with total ω-6 intake.

We present associations between LCω-3PUFA intake and endometrial cancer risk in **Table 3**. Highest compared with the lowest quintiles of total LCω-3PUFA intake (i.e., EPA + DPA + DHA) was associated with a 19% reduction in endometrial cancer risk (HR: 0.81; 95% CI: 0.66, 1.00; *P*-trend = 0.04). Increasing quintiles of EPA, DPA, and DHA intakes were similarly associated with linear 15–23% decreased risks. Total ω-6 and linoleic acid (the predominant ω-6) were not associated with risk; however, increasing levels of AA were associated with linear reductions in endometrial cancer risk (*P*-trend = 0.002). The consumption of α-linolenic acid (18:3ω-3), which does not have notable anti-inflammatory properties, was not associated with risk, and findings from the ω-3:ω-6 ratio differed little from those of individual fatty acids. When food sources of LCω-3PUFAs were examined, a similar reduction in risk was observed (**Table 4**). Women in highest compared with the lowest categories of baked or broiled fish intake had 24% reduced endometrial cancer risk (HR: 0.76; 95% CI: 0.57, 1.01; *P*-trend = 0.003). The findings were driven by the consumption of white fish (*P*-trend = 0.027) and dark or oily fish (*P*-trend = 0.021), respectively. The consumption of shellfish, canned tuna, or fried fish was not associated with risk.

We further examined whether associations were modified when stratified by BMI (**Table 5**). Although a 19% reduction in risk was observed for total LCω-3PUFA intake in the entire cohort, a 41% (HR: 0.59; 95% CI: 0.40, 0.86; *P*-trend = 0.001) reduction was observed in normal-weight women when highest and lowest quintiles of intake were contrasted. No associations were observed between LCω-3PUFA intake and endometrial cancer in overweight or obese women. Associations were similar when overweight and obese women were considered separately (data not shown). *P*-interaction values were significant for EPA, DHA, and total LCω-3PUFAs. The reduction in risk observed for AA did not differ by BMI (*P*-interaction = 0.13). Similarly, when associations between fish intake and endometrial cancer were examined stratified by BMI (**Supplemental Table 1**), inverse associations for baked or broiled fish (summary), white fish, and dark or oily fish were confined to normal-weight women, and *P*-interaction values were significant.

Last, we examined associations between LCω-3PUFA intake and endometrial cancer stratified by histologic subtype (**Table 6**). LCω-3PUFAs were associated with 23–27% linear reductions in risk of type I (endometrioid) cancers but not associated with the risk of type II cancers. *P* values for differences in the associations by subtype were significant. Similar associations were observed for baked or broiled fish intake (**Supplemental Table 2**). Because of the effect modification that we observed in this study, we further stratified associations for type I and II subtypes on BMI. As expected, findings for type I endometrial cancer were similar to those including all incident cases [HR per 1-SD (133-mg/d) increase in total LCω-3PUFAs for BMI <25 was 0.77 (95% CI: 0.64, 0.92) and BMI ≥25 was 0.95 (95% CI: 0.87, 1.04); *P*-interaction = 0.030]. In contrast, associations between total

TABLE 4
Association between fish consumption and endometrial cancer risk in the WHI Observational Study and Clinical Trials (n = 87,360)[1]

	Categories of serving-size adjusted servings/wk					*P*-trend
Baked or broiled fish, servings/wk	0	0.01–0.53	0.54–1.03	1.04–1.84	>1.84	
Cases, *n*	101	312	271	300	269	
HR (95% CI)[2]	1.00 (reference)	0.91 (0.72, 1.13)	0.89 (0.71, 1.12)	0.88 (0.70, 1.10)	0.77 (0.61, 0.97)	0.023
HR (95% CI)[3]	1.00 (reference)	1.04 (0.80, 1.36)	0.93 (0.70, 1.23)	0.89 (0.67, 1.17)	0.76 (0.57, 1.01)	0.003
White fish, servings/wk	0	0.01–0.23	0.24–0.50	0.51–0.81	>0.81	
Cases, *n*	418	251	112	285	187	
HR (95% CI)[2]	1.00 (reference)	0.96 (0.82, 1.12)	0.99 (0.81, 1.22)	1.03 (0.88, 1.19)	0.85 (0.71, 1.01)	0.263
HR (95% CI)[3]	1.00 (reference)	0.97 (0.81, 1.16)	0.90 (0.70, 1.15)	0.96 (0.80, 1.14)	0.75 (0.61, 0.93)	0.027
Dark or oily fish, servings/wk	0	0.01–0.23	0.24–0.34	0.35–0.54	>0.54	
Cases, *n*	706	201	64	116	166	
HR (95% CI)[2]	1.00 (reference)	0.86 (0.74, 1.01)	0.77 (0.59, 0.99)	0.89 (0.73, 1.08)	0.95 (0.81, 1.13)	0.219
HR (95% CI)[3]	1.00 (reference)	0.90 (0.75, 1.07)	0.77 (0.58, 1.02)	0.77 (0.60, 0.98)	0.86 (0.70, 1.05)	0.021
Canned tuna/tuna casserole, servings/wk	0	0.01–0.23	0.24–0.50	0.51–0.81	>0.81	
Cases, *n*	246	258	126	370	253	
HR (95% CI)[2]	1.00 (reference)	0.96 (0.81, 1.15)	0.95 (0.77, 1.18)	1.05 (0.89, 1.23)	0.86 (0.72, 1.03)	0.354
HR (95% CI)[3]	1.00 (reference)	0.97 (0.79, 1.19)	0.95 (0.74, 1.23)	1.06 (0.87, 1.28)	0.90 (0.73, 1.11)	0.688
Shellfish, not fried, servings/wk	0	0.01–0.01	0.02–0.27	0.28–0.54	>0.54	
Cases, *n*	585	71	217	248	132	
HR (95% CI)[2]	1.00 (reference)	1.33 (1.04, 1.71)	1.04 (0.89, 1.22)	1.21 (1.04, 1.41)	1.07 (0.88, 1.29)	0.073
HR (95% CI)[3]	1.00 (reference)	1.43 (1.09, 1.88)	0.97 (0.81, 1.17)	1.04 (0.86, 1.24)	0.88 (0.70, 1.12)	0.535
Fried fish or shellfish, servings/wk	0	0.01–0.23	0.24–0.34	0.35–0.54	>0.54	
Cases, *n*	665	246	71	115	156	
HR (95% CI)[2]	1.00 (reference)	1.04 (0.89, 1.20)	1.07 (0.84, 1.37)	0.82 (0.67, 1.00)	1.02 (0.85, 1.23)	0.486
HR (95% CI)[3]	1.00 (reference)	1.11 (0.94, 1.32)	1.13 (0.85, 1.49)	0.93 (0.74, 1.17)	1.16 (0.93, 1.44)	0.438

[1] *P*-trend values were calculated by treating categorical exposure variables as continuous in regression models. WHI, Women's Health Initiative.
[2] Derived from Cox proportional hazards regression models adjusted for age (time variable) and total energy.
[3] Further adjusted for clinical trial/observational study 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.

TABLE 5
Association between dietary ω-3 PUFA intake and endometrial cancer risk stratified by BMI (in kg/m^2) (n = 87,360)[1]

	Energy-adjusted quintiles of fatty acid intake					
	1	2	3	4	5	*P*-trend
ω-3 Fatty acids						
EPA + DPA + DHA, mg/d	≤56.8	56.9–91.2	91.3–133.9	134.0–205.2	>205.2	
BMI <25, *n* cases	89	80	80	73	70	
HR (95% CI)	1.00 (reference)	0.97 (0.69, 1.37)	0.83 (0.58, 1.18)	0.69 (0.48, 0.99)	0.59 (0.40, 0.86)	0.001
BMI ≥25, *n* cases	176	155	187	168	165	
HR (95% CI)	1.00 (reference)	0.96 (0.75, 1.25)	1.12 (0.88, 1.44)	1.02 (0.80, 1.32)	0.95 (0.74, 1.24)	0.907
P-interaction						0.013
EPA (20:5ω-3), mg/d	≤15.6	15.7–27.4	27.5–41.3	41.4–63.6	>63.6	
BMI <25, *n* cases	88	78	81	78	67	
HR (95% CI)	1.00 (reference)	0.95 (0.68, 1.34)	0.80 (0.57, 1.15)	0.72 (0.50, 1.03)	0.56 (0.38, 0.83)	0.001
BMI ≥25, *n* cases	172	171	161	187	160	
HR (95% CI)	1.00 (reference)	1.15 (0.90, 1.48)	1.02 (0.79, 1.33)	1.17 (0.91, 1.50)	0.97 (0.75, 1.25)	0.881
P-interaction						0.013
DPA (22:5ω-3), mg/d	≤6.8	6.9–10.7	10.8–15.2	15.3–22.2	>22.2	
BMI <25, *n* cases	87	79	88	70	68	
HR (95% CI)	1.00 (reference)	0.89 (0.63, 1.25)	0.93 (0.66, 1.30)	0.61 (0.42, 0.90)	0.70 (0.48, 1.02)	0.012
BMI ≥25, *n* cases	180	171	160	170	170	
HR (95% CI)	1.00 (reference)	1.09 (0.85, 1.39)	0.94 (0.73, 1.21)	0.93 (0.72, 1.20)	0.93 (0.72, 1.20)	0.297
P-interaction						0.143
DHA (22:6ω-3), mg/d	≤32.8	32.9–51.9	52.0–76.8	76.9–121.0	>121.0	
BMI <25, *n* cases	96	81	71	69	75	
HR (95% CI)	1.00 (reference)	0.86 (0.61, 1.20)	0.68 (0.48, 0.97)	0.57 (0.40, 0.82)	0.53 (0.37, 0.77)	<0.001
BMI ≥25, *n* cases	185	147	189	167	163	
HR (95% CI)	1.00 (reference)	0.92 (0.71, 1.19)	1.12 (0.88, 1.43)	0.97 (0.76, 1.25)	0.94 (0.73, 1.21)	0.797
P-interaction						0.003
ALA (18:3ω-3), mg/d	≤921.6	921.7–1130.6	1130.7–1333.1	1333.2–1640.0	>1640.0	
BMI <25, *n* cases	87	74	76	79	76	
HR (95% CI)	1.00 (reference)	0.95 (0.66, 1.35)	0.98 (0.68, 1.41)	1.15 (0.81, 1.64)	1.13 (0.78, 1.62)	0.311
BMI ≥25, *n* cases	195	169	144	159	184	
HR (95% CI)	1.00 (reference)	0.93 (0.73, 1.19)	0.75 (0.58, 0.98)	0.89 (0.70, 1.15)	0.89 (0.70, 1.14)	0.352
P-interaction						0.310
ω-6 Fatty acids						
LA + AA, mg/d	≤8328.5	8328.6–10,061.7	10,061.8–11,539.7	11,539.8–13,494.5	>13,494.5	
BMI <25, *n* cases	85	85	71	75	76	
HR (95% CI)	1.00 (reference)	0.94 (0.66, 1.33)	1.00 (0.69, 1.43)	1.21 (0.84, 1.75)	1.46 (1.01, 2.10)	0.024
BMI ≥25, *n* cases	182	148	158	164	199	
HR (95% CI)	1.00 (reference)	0.75 (0.58, 0.97)	0.82 (0.63, 1.05)	0.82 (0.64, 1.06)	0.95 (0.75, 1.21)	0.999
P-interaction						0.159
LA (18:2ω-6), mg/d	≤8235.9	8236.0–9962.1	9962.2–11,438.1	11,438.2–13,391.3	>13,391.3	
BMI <25, *n* cases	83	87	71	76	75	
HR (95% CI)	1.00 (reference)	0.93 (0.66, 1.32)	0.99 (0.69, 1.42)	1.22 (0.84, 1.75)	1.41 (0.98, 2.04)	0.032
BMI ≥25, *n* cases	184	146	159	163	199	
HR (95% CI)	1.00 (reference)	0.72 (0.56, 0.93)	0.81 (0.63, 1.05)	0.80 (0.62, 1.04)	0.94 (0.74, 1.20)	0.957
P-interaction						0.173
AA (20:4ω-6), mg/d	≤61.5	61.6–80.9	81.0–99.8	99.9–127.5	>127.5	
BMI <25, *n* cases	115	91	80	58	48	
HR (95% CI)	1.00 (reference)	0.73 (0.53, 1.01)	0.77 (0.55, 1.07)	0.55 (0.38, 0.81)	0.67 (0.46, 0.99)	0.007
BMI ≥25, *n* cases	188	145	148	166	204	
HR (95% CI)	1.00 (reference)	0.81 (0.63, 1.04)	0.78 (0.60,1.00)	0.80 (0.62,1.02)	0.80 (0.63,1.02)	0.105
P-interaction						0.130
ω-3:ω-6						
Ratio of EPA + DPA + DHA to LA + AA, mg/d	≤0.005	0.006–0.008	0.009–0.013	0.014–0.021	>0.021	
BMI <25, *n* cases	82	85	72	76	77	
HR (95% CI)	1.00 (reference)	1.09 (0.77, 1.55)	0.81 (0.56, 1.17)	0.67 (0.46, 0.97)	0.66 (0.46, 0.97)	0.002
BMI ≥25, *n* cases	184	159	169	181	158	
HR (95% CI)	1.00 (reference)	0.92 (0.71, 1.18)	0.95 (0.74, 1.22)	1.09 (0.85, 1.39)	0.90 (0.70, 1.17)	0.916
P-interaction						0.030

[1]HRs (95% CIs) were derived from Cox proportional hazards regression models adjusted for age (time variable), clinical trial/observational study 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, history of diabetes, and total energy. *P*-trend values were calculated by treating categorical exposure variables as continuous in regression models. *P*-interaction values were calculated by using the likelihood ratio test. AA, arachidonic acid; ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid.

LCω-3PUFAs and type II endometrial cancer were not modified by BMI [<25: HR, 1.15 (95% CI: 0.96, 1.39); ≥25: HR, 1.08 (95% CI: 0.89, 1.31); *P* interaction = 0.283)].

DISCUSSION

In this large, prospective study of postmenopausal women across the United States, dietary intakes of LCω-3PUFAs and fish were associated with reduced risk of endometrial cancer. Our findings confirmed a reduction in risk restricted in normal-weight women but little association in overweight or obese women. The benefit was further restricted to the incidence of type I endometrial cancer subtypes, which are the most-common and least-aggressive types, again in normal-weight women.

To our knowledge, our trial is the second prospective study and the third study overall to examine the association between individual LCω-3PUFAs and endometrial cancer risk. In our previous report in women participating in the VITAL cohort in Washington State, we showed that LCω-3PUFAs were associated with decreased risks in normal-weight women [quintiles 5 compared with 1: EPA + DHA, HR of 0.39 (95% CI: 0.16, 0.97); *P*-trend = 0.046] and increased risks in overweight and obese women (HR: 2.75; 95% CI: 1.62, 4.68; *P*-trend < 0.001, *P* interaction = 0.004) (17). Although we did not analyze DPA in the previous report, a subsequent re-analysis of data with DPA included made little difference in HRs (unpublished data). In a population-based case-control study that was based in Connecticut, Arem et al. (32) reported similar reductions in endometrial cancer risk as we report here [quintile 4 compared with quintile 1: EPA, OR of 0.57 (95% CI: 0.39, 0.84); DHA, OR of 0.64 (95% CI: 0.44, 0.94); *P*-trend for each < 0.04]. The authors did not examine effect modification by body size. The findings from the current study provide additional support for an inverse association between LCω-3PUFAs and endometrial cancer in normal-weight women; however, we did not replicate increased risk in overweight and obese women as reported in the VITAL cohort.

Although few studies examined specific LCω-3PUFAs, we (17) and other authors (33–42) examined associations between fish intake and endometrial cancer risk. Several previous case-control studies failed to adjust for energy intake or body size or did not exclude histories of hysterectomy from control groups (43). Of the few prospective studies (17, 42, 44), findings were inconsistent. Much like the current study, our findings for LCω-3PUFAs in the VITAL cohort were mirrored in our analysis of their food sources whereby intakes of baked or broiled fish were inversely associated with endometrial cancer risk in normal-weight women [highest compared with lowest categories: HR, 0.43 (95% CI: 0.16, 1.13)] and positively associated with risk in overweight or obese women (HR: 2.87; 95% CI: 1.27, 6.51; *P* interaction = 0.015) (17), whereas we reported similar reductions in risk of baked or broiled fish intake in normal-weight women but little evidence of an association in overweight or obese women. Different from our findings in the current study, authors of the NIH-AARP Diet Study of fish (42) and Iowa Women's Health Study of seafood intakes (44) reported no association or elevated risks, respectively. Only the NIH-AARP Diet Study examined the interaction between fish intake and body size (42); no interaction was shown.

To our knowledge, this is the only study to examine associations between LCω-3PUFAs and type II endometrial cancer or associations for different histologic types further stratified by BMI. In our previous report, the restriction of the analysis to type I cancers nominally strengthened our findings, but in that study, there were very few type II cancers (n = 35). There is some debate as to whether established risk factors for endometrial cancer differ by histologic subtype (45). Our findings here support a difference at least in the case of dietary LCω-3PUFA exposure.

We know of no clear explanation why results for overweight women differed in the current study from those in our previous report, especially because of the consistency of findings for normal-weight women between the studies. Study populations were mostly similar, and associations between participant characteristics and LCω-3PUFAs were similar between studies. In addition, the VITAL cohort used the same FFQ as used for the WHI. The main differences between the studies, besides sample sizes, were that the WHI had a longer follow-up and measured (as opposed to self-reported) height and weight.

Anti-inflammatory properties of LCω-3PUFAs may broadly explain the anti-cancer benefit observed in the current study; however, the restriction of a benefit to normal-weight women is not easily explained. An increased body size is associated with increased inflammation and endogenous sex hormones. It may be that the anti-inflammatory effects of ω-3 are overshadowed in a highly inflammatory environment or increased presence of sex hormones. This possibility was supported by an analysis of the NHANES study, which showed that the use of fish oil and other anti-inflammatory supplements was associated with reduced high-sensitivity C-reactive protein in individuals with BMI <25 but not in those with higher BMI (46). However, studies of nonsteroidal anti-inflammatory drugs suggested an inverse association in obese women only (47). There is limited evidence that ω-3 is associated with endogenous sex hormones (48), but findings from a number of small controlled feeding trials were inconsistent (49–53). That the association between LCω-3PUFA and endometrial cancer was restricted further to type I cancers, which are considered estrogen-responsive (54), strongly suggested interrelations in fatty acids, sex hormones, inflammation, and cancer risk.

This study had several limitations that should be considered. Chief of them was that dietary data from this study were self-reported. A self-reported diet is subjective and prone to measurement error (55); however, because of the prospective nature of the study and the attenuating effect of nondifferential measurement error, significant associations reported in the current study were despite this error. More importantly, the imperfect measurement of energy intakes would have resulted in residual confounding, which would likely have resulted in negative confounding and, again, an underestimation of true risk. In addition, because of the number of statistical tests, it remains possible that some findings may have been the result of chance. Last, we note that our findings were strongest for intakes of white fish (465 mg LCω-3PUFAs/serving in the University of Minnesota's Nutrient Data System for Research) rather than dark or oily fish (1140 mg/serving), which differed in their ω-3 contents. Canned tuna is not a major source of long-chain ω-3 in the nutrient database. These results left open several possibilities as follows: *1*) some other component of fish, aside from the fatty

TABLE 6
Association between dietary ω-3 PUFA intake and endometrial cancer, defined by histopathologic subtype (n = 87,360)[1]

	Energy-adjusted quintiles of fatty acid intake					
	1	2	3	4	5	P-trend
ω-3 Fatty acids						
EPA + DPA + DHA, mg/d	≤56.8	56.9–91.2	91.3–133.9	134.0–205.2	>205.2	
Type I, n cases	226	207	220	190	189	
HR (95% CI)	1.00 (reference)	1.01 (0.81, 1.25)	0.99 (0.79, 1.23)	0.80 (0.64, 1.01)	0.77 (0.61, 0.98)	0.006
Type II, n cases	31	25	40	44	40	
HR (95% CI)	1.00 (reference)	0.86 (0.46, 1.60)	1.26 (0.71, 2.23)	1.68 (0.98, 2.89)	1.15 (0.64, 2.07)	0.146
P-difference						0.001
EPA (20:5ω-3), mg/d	≤15.6	15.7–27.4	27.5–41.3	41.4–63.6	>63.6	
Type I, n cases	224	215	197	215	181	
HR (95% CI)	1.00 (reference)	1.09 (0.87, 1.35)	0.90 (0.72, 1.13)	0.91 (0.72, 1.14)	0.75 (0.59, 0.95)	0.006
Type II, n cases	28	30	40	44	38	
HR (95% CI)	1.00 (reference)	1.10 (0.59, 2.05)	1.44 (0.80, 2.57)	1.78 (1.01, 3.13)	1.30 (0.71, 2.37)	0.139
P-difference						0.002
DPA (22:5ω-3), mg/d	≤6.8	6.9–10.7	10.8–15.2	15.3–22.2	>22.2	
Type I, n cases	235	206	208	197	186	
HR (95% CI)	1.00 (reference)	0.99 (0.79, 1.23)	0.92 (0.74, 1.15)	0.74 (0.59, 0.93)	0.77 (0.61, 0.97)	0.002
Type II, n cases	27	34	36	35	48	
HR (95% CI)	1.00 (reference)	1.17 (0.64, 2.14)	1.35 (0.75, 2.43)	1.35 (0.75, 2.43)	1.63 (0.92, 2.87)	0.083
P-difference						<0.001
DHA (22:6ω-3), mg/d	≤32.8	32.9–51.9	52.0–76.8	76.9–121.0	>121.0	
Type I, n cases	240	198	216	188	190	
HR (95% CI)	1.00 (reference)	0.92 (0.74, 1.14)	0.92 (0.74, 1.15)	0.73 (0.58, 0.92)	0.73 (0.58, 0.92)	0.001
Type II, n cases	32	26	40	41	41	
HR (95% CI)	1.00 (reference)	0.77 (0.41, 1.45)	1.33 (0.77, 2.31)	1.48 (0.86, 2.55)	1.08 (0.60, 1.93)	0.240
P-difference						0.002
ALA (18:3ω-3), mg/d	≤921.6	921.7–1130.6	1130.7–1333.1	1333.2–1640.0	>1640.0	
Type I, n cases	227	207	184	194	220	
HR (95% CI)	1.00 (reference)	0.99 (0.80, 1.23)	0.80 (0.63, 1.02)	0.98 (0.79, 1.23)	0.98 (0.79, 1.23)	0.871
Type II, n cases	42	32	33	41	32	
HR (95% CI)	1.00 (reference)	0.89 (0.50, 1.57)	1.14 (0.66, 1.97)	1.33 (0.78, 2.25)	0.91 (0.51, 1.61)	0.709
P-difference						0.545
ω-6 Fatty acids						
LA + AA, mg/d	≤8328.5	8328.6–10,061.7	10,061.8–11,539.7	11,539.8–13,494.5	>13,494.5	
Type I, n cases	216	192	195	194	235	
HR (95% CI)	1.00 (reference)	0.80 (0.64, 1.01)	0.93 (0.74, 1.17)	0.92 (0.73, 1.16)	1.15 (0.92, 1.43)	0.118
Type II, n cases	40	36	30	40	34	
HR (95% CI)	1.00 (reference)	1.00 (0.59, 1.68)	0.77 (0.43, 1.37)	1.14 (0.67, 1.95)	0.83 (0.46, 1.47)	0.731
P-difference						0.532
LA (18:2ω-6), mg/d	≤8235.9	8236.0–9962.1	9962.2–11,438.1	11,438.2–13,391.3	>13,391.3	
Type I, n cases	215	193	196	194	234	
HR (95% CI)	1.00 (reference)	0.78 (0.62, 0.98)	0.92 (0.73, 1.16)	0.91 (0.72, 1.15)	1.13 (0.90, 1.40)	0.147
Type II, n cases	41	35	30	40	34	
HR (95% CI)	1.00 (reference)	1.00 (0.59, 1.68)	0.77 (0.44, 1.37)	1.14 (0.67, 1.95)	0.83 (0.46, 1.47)	0.733
P-difference						0.579
AA (20:4ω-6), mg/d	≤61.5	61.6–80.9	81.0–99.8	99.9–127.5	>127.5	
Type I, n cases	256	189	192	186	209	
HR (95% CI)	1.00 (reference)	0.75 (0.60, 0.93)	0.78 (0.63, 0.97)	0.68 (0.55, 0.86)	0.74 (0.59, 0.92)	0.004
Type II, n cases	34	43	31	31	41	
HR (95% CI)	1.00 (reference)	1.34 (0.79, 2.28)	0.90 (0.51, 1.61)	1.04 (0.59, 1.82)	1.01 (0.58, 1.77)	0.667
P-difference						0.317
ω-3:ω-6						
Ratio of EPA + DPA + DHA to LA + AA, mg/d	≤0.005	0.006–0.008	0.009–0.013	0.014–0.021	>0.021	
Type I, n cases	233	214	187	212	186	
HR (95% CI)	1.00 (reference)	0.97 (0.78, 1.20)	0.80 (0.64, 1.01)	0.86 (0.69, 1.08)	0.73 (0.58, 0.92)	0.006
Type II, n cases	27	27	45	39	42	
HR (95% CI)	1.00 (reference)	1.12 (0.58, 2.13)	1.97 (1.10, 3.53)	1.65 (0.90, 3.01)	1.61 (0.88, 2.96)	0.069
P-difference						<0.001

[1]Type I cancers were predominantly carcinomas and endometrioid adenocarcinomas (n = 1032). Type II cancers included serous, papillary, or clear cell carcinomas and mixed tumors (i.e., carcinosarcomas) (n = 180). Regression models for type I cancers censor type II tumors and other subtypes (n = 41), and models for type II tumors censor type I and other subtypes at their respective times at diagnosis. HRs (95% CI) were derived from Cox proportional hazards regression models adjusted for age (time variable), clinical trial/observational study 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, history of diabetes, and total energy. P-trend values were calculated by treating categorical exposure variables as continuous in regression models. P values for the difference in associations between fatty acids and endometrial cancer subtypes were compared by using a case-only–adjusted logistic regression model. AA, arachidonic acid; ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid.

acid content, explains the associations shown in the current study; *2*) there is residual confounding by other healthy behaviors in normal-weight women that are difficult to measure and may explain these results; or *3*) perhaps most likely, women did not accurately recall their consumption of specific fish types [for instance, oily fish with lightly colored flesh (e.g., mackerel or swordfish) may have been recalled as white fish].

Limitations notwithstanding, this study had several strengths including its prospective design, long duration, and completeness of follow-up, comprehensive measurement of endometrial cancer risk factors, and an FFQ that was designed to better measure fat intakes. With >1200 endometrial cancer cases, this study was, to our knowledge, by far the largest and best-powered study to examine these associations with endometrial cancer risk, and it is the first to quantify associations with type II endometrial cancer.

In conclusion, in this prospective study of postmenopausal women in the United States, intakes of LCω-3PUFAs and fish were associated with reduced risks of endometrial cancer in normal-weight women only, which confirmed similar findings in normal-weight women in a previous cohort (17). Our findings support a role for LCω-3PUFA and fish intakes in endometrial cancer prevention. Additional studies that use biomarkers of ω-3 intake are needed to more-accurately estimate their effects on endometrial cancer risk.

A short list of WHI investigators is as follows—program office: Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller (National Heart, Lung, and Blood Institute, Bethesda, MD); clinical coordinating center: Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg (Fred Hutchinson Cancer Research Center, Seattle, WA); investigators and academic centers: JoAnn E Manson (Brigham and Women's Hospital, Harvard Medical School, Boston, MA), Barbara V Howard (MedStar Health Research Institute/Howard University, Washington, DC), Marcia L Stefanick (Stanford Prevention Research Center, Stanford, CA), Rebecca Jackson (The Ohio State University, Columbus, OH), Cynthia A Thomson (University of Arizona, Tucson/Phoenix, AZ), Jean Wactawski-Wende (University at Buffalo, Buffalo, NY), Marian Limacher (University of Florida, Gainesville/Jacksonville, FL), Robert Wallace (University of Iowa, Iowa City/Davenport, IA), Lewis Kuller (University of Pittsburgh, Pittsburgh, PA), and Sally Shumaker (Wake Forest University School of Medicine, Winston-Salem, NC); and the Women's Health Initiative Memory Study: Sally Shumaker (Wake Forest University School of Medicine, Winston-Salem, NC).

The authors' responsibilities were as follows—TMB: designed the research and wrote the manuscript; RJR and JL: analyzed data; MLK, LAW, TSO, DEC, MAB, EW, and MLN: assisted in the research design and analysis plan; MLN: had primary responsibility for the final content of the manuscript; and all authors: contributed to the manuscript writing and gave approval of the final draft of the manuscript for submission None of the authors reported a conflict of interest related to the study.

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