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Original Contribution

Associations of Dietary Long-Chain ω-3 Polyunsaturated Fatty Acids and Fish Consumption With Endometrial Cancer Risk in the Black Women's Health Study

Theodore M. Brasky*, Todd R. Sponholtz, Julie R. Palmer, Lynn Rosenberg, Edward A. Ruiz-Narváez, and Lauren A. Wise

* Correspondence to Dr. Theodore M. Brasky, Ohio State University Comprehensive Cancer Center, 1590 North High Street, Suite 525, Columbus, OH 43209 (e-mail: Theodore.Brasky@osumc.edu).

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Dietary long-chain (LC) ω-3 polyunsaturated fatty acids (PUFAs), which derive primarily from intakes of fatty fish, are thought to inhibit inflammation and de novo estrogen synthesis. This study prospectively examined the associations of dietary LC ω-3 PUFAs and fish with endometrial cancer risk in 47,602 African-American women living in the United States, aged 21–69 years at baseline in 1995, and followed them until 2013 ($n = 282$ cases). Multivariable-adjusted Cox regression models estimated hazard ratios and 95% confidence intervals for associations of LC ω-3 PUFA (quintiled) and fish (quartiled) intake with endometrial cancer risk, overall and by body mass index (BMI; weight (kg)/height $(m)^2$). The hazard ratio for quintile 5 of total dietary LC ω-3 PUFAs versus quintile 1 was 0.79 (95% confidence interval (CI): 0.51, 1.24); there was no linear trend. Hazard ratios for the association were smaller among normal-weight women (BMI <25: hazard ratio (HR) = 0.53, 95% CI: 0.18, 1.58) than among overweight/obese women (BMI ≥25: HR = 0.88, 95% CI: 0.54, 1.43), but these differences were not statistically significant. Fish intake was also not associated with risk (quartile 4 vs. quartile 1: HR = 0.86, 95% CI: 0.56, 1.31). Again hazard ratios were smaller among normal-weight women (HR = 0.65) than among overweight/obese women (HR = 0.94). While compatible with no association, the hazard ratios observed among leaner African-American women are similar to those from recent prospective studies conducted in predominantly white populations.

African-American women; docosahexaenoic acid; eicosapentaenoic acid; endometrial cancer; fish; uterine cancer; women's reproductive health

Abbreviations: BMI, body mass index; BWHS, Black Women's Health Study; CI, confidence interval; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; HR, hazard ratio; LC, long-chain; PUFA, polyunsaturated fatty acid; VITAL, Vitamins and Lifestyle; WHI, Women's Health Initiative.

Endometrial cancer is the fourth most common cancer and the leading gynecological malignancy diagnosed in US women (1). Incidence rates are about 9% lower for African-American women relative to white women (2), but a recent study of Surveillance, Epidemiology, and End Results data that corrected for hysterectomy prevalence indicated a higher incidence in black women (3). African-American women are twice as likely to be diagnosed with an aggressive phenotype (4–6) and more likely to die from the disease (2).

Inflammation may be an important factor in endometrial cancer etiology. Prospective studies have shown that increases in circulating biomarkers of inflammation are associated with increases in endometrial cancer risk (7–9). In contrast, studies of nonsteroidal antiinflammatory drugs suggest a reduction in endometrial cancer risk (10). Higher intakes of long-chain (LC) ω-3 polyunsaturated fatty acids (PUFAs), which derive primarily from the consumption of fatty fish and which may act through similar biological mechanisms as nonsteroidal antiinflammatory drugs, have been associated with reduced inflammation in observational studies (11, 12) and randomized clinical trials (13–15).

The associations between dietary intakes of LC ω-3 PUFAs and endometrial cancer risk have been assessed in 2 prospective studies to date (16, 17). We previously reported that

Table 1. Distribution of Baseline Dietary Total Long-Chain ω-3 Fatty Acid Intake According to Participants' Characteristics in the Black Women's Health Study ($n = 47,602$), Overall and by Body Mass Index, 1995–2013

Characteristic	Least-Squares Mean EPA + DPA + DHA Intake From Diet, mg/day[a]						
	All Participants			BMI[b] <25		BMI ≥25	
	No. of Women	Mean	95% CI	Mean	95% CI	Mean	95% CI
Age, years[c]							
21–30	14,030	105.9	104.4, 107.5	105.4	103.3, 107.4	106.7	104.5, 108.9
31–40	17,307	122.1	120.8, 123.5	122.7	120.7, 124.8	121.7	119.9, 123.5
41–50	9,931	132.0	130.2, 133.8	131.4	128.4, 134.5	132.2	130.0, 134.5
51–60	3,064	138.6	135.4, 141.9	135.3	129.0, 141.7	139.6	135.8, 143.4
61–69	1,093	137.8	132.4, 143.3	129.1	118.7, 139.6	140.8	134.3, 147.2
US region							
Northeast	13,098	127.1	125.5, 128.6	124.4	122.0, 126.8	129.0	126.9, 131.1
South	13,677	120.7	119.2, 122.2	117.8	115.5, 120.1	122.8	120.7, 124.8
Midwest	10,278	115.7	114.0, 117.5	111.3	108.5, 114.0	118.7	116.4, 121.0
West	8,317	117.3	115.3, 119.2	116.9	114.0, 119.7	117.3	114.7, 120.0
Education							
High school graduate or less	6,986	108.6	106.4, 110.7	106.0	102.2, 110.0	110.4	107.8, 113.0
Some college	16,690	118.8	117.4, 120.2	114.3	112.2, 116.5	121.8	120.0, 123.6
College graduation or advanced degree	21,432	126.3	125.1, 127.5	123.2	121.5, 125.0	128.6	126.9, 130.3
BMI							
<18.5	840	105.0	98.9, 111.2				
18.5–24.9	17,802	121.0	119.7, 122.4				
25–29.9	13,645	124.1	122.6, 125.6				
30–34.9	6,807	119.8	117.6, 121.9				
35–39.9	3,189	115.3	112.1, 118.4				
≥40	2,596	116.1	112.6, 119.6				
Vigorous physical activity, hours/week							
None	13,444	108.2	106.7, 109.8	104.8	102.2, 107.5	110.6	108.6, 112.5
<5	24,098	124.2	123.0, 125.3	119.7	118.0, 121.4	127.4	125.9, 129.0
≥5	6,235	134.0	131.7, 136.3	130.9	127.8, 133.9	136.4	133.0, 139.7
Alcohol consumption, drinks/week							
0	32,694	117.2	116.2, 118.2	115.1	113.6, 116.6	118.8	117.5, 120.1
0.1–1.9	3,389	124.6	121.6, 127.7	124.8	119.9, 129.7	124.7	120.8, 128.7
≥2.0	9,058	132.1	130.2, 134.0	127.3	124.4, 130.2	135.5	133.0, 138.0
Smoking, pack-years							
0	30,793	119.3	118.3, 120.4	117.4	115.9, 118.9	120.7	119.3, 122.1
0.1–4.0	5,272	126.7	124.2, 129.2	124.1	120.1, 128.1	128.5	125.3, 131.6
4.1–13.9	4,836	124.8	122.2, 127.4	120.8	116.6, 125.1	127.2	124.0, 130.5
≥14.0	3,697	118.0	114.9, 121.1	111.1	105.7, 116.4	121.8	118.0, 125.5
Fruit consumption, servings/week							
≤2	18,272	108.4	107.1, 109.8	106.3	104.3, 108.4	109.9	108.1, 111.6
3–4	8,988	124.3	122.4, 126.2	121.3	118.4, 124.2	126.4	123.9, 128.9
4–6	10,336	131.6	129.8, 133.3	128.5	125.8, 131.1	133.8	131.5, 136.2
≥7	6,659	134.1	131.9, 136.3	130.4	127.0, 133.7	136.8	133.9, 139.7
Vegetable consumption, servings/week							
≤2	11,034	102.2	100.5, 104.0	99.3	96.7, 102.0	104.2	102.0, 106.5
3–4	10,937	117.9	116.2, 119.6	115.8	113.2, 118.4	119.3	117.0, 121.6
4–6	14,559	127.6	126.1, 129.0	126.5	124.2, 128.7	128.4	126.4, 130.3
≥7	8,036	138.6	136.6, 140.6	132.6	129.6, 135.7	142.8	140.2, 145.5

Table continues

Table 1. Continued

Characteristic	Least-Squares Mean EPA + DPA + DHA Intake From Diet, mg/day[a]						
	All Participants			BMI[b] <25		BMI ≥25	
	No. of Women	Mean	95% CI	Mean	95% CI	Mean	95% CI
Menopausal status							
Premenopausal	40,452	122.1	121.2, 123.0	119.4	118.0, 120.7	124.0	122.7, 125.2
Perimenopausal	514	116.5	108.5, 124.5	105.3	90.3, 120.3	121.8	112.3, 131.3
Postmenopausal	4,440	109.2	105.8, 112.6	101.4	95.3, 107.6	113.4	109.3, 117.5
Age at menarche, years							
9–11	12,643	120.2	118.6, 121.7	119.1	116.3, 121.8	121.1	119.2, 123.1
12–13	23,986	120.8	119.6, 121.9	118.7	116.9, 120.4	122.3	120.7, 123.8
≥14	8,590	121.8	119.8, 123.7	116.1	113.4, 118.8	126.9	124.1, 129.6
Age at menopause, years							
<47	1,477	111.2	106.3, 116.2	100.2	91.3, 109.0	116.9	110.9, 122.9
47–51	1,430	110.9	105.7, 116.1	104.2	94.7, 113.8	114.6	108.3, 120.9
≥52	1,105	101.8	95.8, 107.8	98.8	87.0, 110.6	104.2	97.1, 111.2
Pre- or perimenopausal	40,966	121.8	120.9, 122.8	119.1	117.8, 120.4	123.8	122.5, 125.0
Parity							
Nulliparous or nulligravid	17,896	125.5	124.0, 126.9	123.5	121.5, 125.5	126.6	124.6, 128.7
1	10,021	123.0	121.3, 124.8	117.9	115.1, 120.6	126.6	124.2, 129.0
2	9,773	118.5	116.7, 120.3	114.0	111.0, 117.0	121.4	119.1, 123.8
3	4,648	112.2	109.6, 114.9	107.6	103.0, 112.3	115.1	111.8, 118.4
≥4	3,007	105.7	102.3, 109.1	96.8	90.1, 103.4	110.1	106.1, 114.1
Age at first birth, years							
Nulliparous or nulligravid	17,896	124.8	123.4, 126.2	123.0	121.0, 125.0	125.9	123.9, 127.9
<20	8,771	117.1	115.2, 119.0	111.3	108.0, 114.7	120.5	118.1, 122.8
20–24	9,671	116.4	114.6, 118.2	112.2	109.2, 115.2	119.1	116.8, 121.5
≥25	8,774	120.8	118.9, 122.7	117.2	114.2, 120.2	123.2	120.7, 125.8
Duration of combined hormone therapy, years							
0	43,840	120.5	119.7, 121.4	117.9	116.6, 119.2	122.4	121.2, 123.5
0.1–2.4	924	131.4	125.3, 137.5	126.1	115.2, 136.9	134.5	127.1, 141.9
≥2.5	625	124.2	116.8, 131.6	122.4	110.6, 134.2	125.6	116.1, 135.2
Duration of unopposed estrogen therapy, years							
0	44,789	120.8	120.0, 121.7	118.2	116.9, 119.5	122.7	121.6, 123.9
0.1–2.4	431	114.2	105.5, 122.8	110.5	94.2, 126.9	116.4	106.1, 126.6
≥2.5	174	119.4	105.6, 133.1	107.0	85.9, 128.0	128.2	110.0, 146.4
Duration of oral contraceptive use, years							
0	6,577	116.3	114.1, 118.5	115.3	11.8, 118.8	117.2	114.3, 120.0
0.1–5	23,990	120.3	119.1, 121.4	117.1	115.3, 118.8	122.5	121.0, 124.0
5.1–10	8,942	123.3	121.4, 125.2	120.2	117.5, 123.0	125.5	122.9, 128.1
>10	5,854	124.1	121.8, 126.5	121.6	118.0, 125.1	126.0	122.9, 129.1
History of diabetes							
No	44,001	120.7	119.8, 121.5	118.0	116.8, 119.3	122.5	121.4, 123.7
Yes	1,424	124.3	119.5, 129.1	124.5	112.1, 136.8	125.7	120.4, 130.9

Abbreviations: BMI, body mass index; CI, confidence interval; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid.

[a] Adjusted for age and energy intake.

[b] Weight (kg)/height $(m)^2$.

[c] Adjusted for energy intake only.

Table 2. Associations Between Dietary ω-3 PUFA Intake and Endometrial Cancer Risk in the Black Women's Health Study, Overall and by Body Mass Index, 1995–2013

Fatty Acid and Quintile of Intake[a]	No. of Cases	Adjusted[b]		Further Adjusted[b,c]		Body Mass Index[d]					
						<25			≥25		
		HR	95% CI	HR	95% CI	No. of Cases	HR[b,c]	95% CI	No. of Cases	HR[b,c]	95% CI
ω-3 Fatty Acids											
EPA (20:5ω3)											
1	65	1.00	Referent	1.00	Referent	15	1.00	Referent	49	1.00	Referent
2	48	0.73	0.49, 1.10	0.66	0.42, 1.05	6	0.56	0.19, 1.60	42	0.68	0.41, 1.15
3	49	0.76	0.51, 1.14	0.77	0.50, 1.20	15	1.01	0.41, 2.46	33	0.71	0.43, 1.18
4	57	0.76	0.52, 1.12	0.84	0.55, 1.29	15	1.01	0.43, 2.40	42	0.80	0.49, 1.31
5	56	0.67	0.45, 0.98	0.72	0.47, 1.10	11	0.43	0.15, 1.21	44	0.82	0.51, 1.31
P-trend[e]		0.080		0.363			0.358			0.659	
P-interaction[f]								0.620			
DPA (22:5ω3)											
1	60	1.00	Referent	1.00	Referent	12	1.00	Referent	47	1.00	Referent
2	44	0.79	0.52, 1.19	0.92	0.58, 1.46	12	1.45	0.56, 3.79	32	0.82	0.48, 1.39
3	49	0.87	0.58, 1.30	0.88	0.56, 1.41	10	0.87	0.29, 2.60	39	0.92	0.55, 1.55
4	64	0.96	0.66, 1.41	1.16	0.76, 1.76	20	2.18	0.90, 5.26	43	0.97	0.60, 1.58
5	56	0.79	0.54, 1.16	0.88	0.57, 1.36	8	0.55	0.18, 1.72	47	0.98	0.61, 1.57
P-trend		0.525		0.956			0.756			0.838	
P-interaction								0.738			
DHA (22:6ω3)											
1	57	1.00	Referent	1.00	Referent	13	1.00	Referent	43	1.00	Referent
2	49	0.88	0.58, 1.33	1.01	0.64, 1.60	10	1.18	0.44, 3.16	39	0.98	0.58, 1.64
3	46	0.69	0.45, 1.06	0.69	0.42, 1.13	12	0.98	0.35, 2.71	34	0.63	0.36, 1.11
4	66	0.96	0.66, 1.42	1.17	0.76, 1.78	16	1.49	0.59, 3.74	49	1.10	0.68, 1.79
5	57	0.75	0.51, 1.10	0.84	0.54, 1.30	11	0.52	0.17, 1.55	45	0.94	0.58, 1.53
P-trend		0.287		0.699			0.412			0.947	
P-interaction								0.541			
Total long-chain ω-3 PUFAs (EPA + DPA + DHA)											
1	59	1.00	Referent	1.00	Referent	13	1.00	Referent	45	1.00	Referent
2	50	0.94	0.63, 1.41	0.94	0.60, 1.47	10	1.18	0.44, 3.14	40	0.87	0.52, 1.46
3	44	0.72	0.47, 1.10	0.74	0.46, 1.19	11	0.88	0.31, 2.52	33	0.71	0.41, 1.21
4	65	0.97	0.66, 1.43	1.13	0.74, 1.72	17	1.67	0.67, 4.16	47	1.03	0.63, 1.67
5	55	0.75	0.50, 1.10	0.79	0.51, 1.24	11	0.53	0.18, 1.58	43	0.88	0.54, 1.43
P-trend		0.226		0.605			0.516			0.899	
P-interaction								0.686			

Table continues

intakes of total LC ω-3 PUFAs were associated with 41%–61% linear reductions in endometrial cancer risk among normal-weight (body mass index (BMI; weight (kg)/height $(m)^2$) <25) women in the Vitamins and Lifestyle (VITAL) Study cohort (16) and the Women's Health Initiative (WHI) (17). However, in the VITAL Study, we reported 175% linear increases in endometrial cancer risk among overweight/obese women (16) which were not subsequently replicated in the much larger WHI (17). In each study, associations reported for fish intake (especially baked or broiled fish) were similar to those reported for the LC ω-3 PUFAs. These results notwithstanding, African-American women comprised only a small fraction of the study populations; thus, the extent to which previous findings are generalizable to black women remains unclear.

In the present study, we assessed dietary LC ω-3 PUFAs and fish in relation to endometrial cancer risk, overall and by BMI, in the Black Women's Health Study (BWHS), a large prospective cohort study of African-American women.

Table 2. Continued

Fatty Acid and Quintile of Intake[a]	No. of Cases	Adjusted[b]		Further Adjusted[b,c]		Body Mass Index[d]					
						<25			≥25		
		HR	95% CI	HR	95% CI	No. of Cases	HR[b,c]	95% CI	No. of Cases	HR[b,c]	95% CI
ALA (18:3ω3)											
1	54	1.00	Referent	1.00	Referent	13	1.00	Referent	41	1.00	Referent
2	49	0.86	0.57, 1.29	0.94	0.60, 1.48	9	0.82	0.32, 2.11	40	0.94	0.56, 1.59
3	59	0.97	0.66, 1.43	1.12	0.73, 1.72	15	1.14	0.47, 2.78	44	1.11	0.68, 1.82
4	52	0.71	0.47, 1.07	0.70	0.44, 1.11	16	0.84	0.33, 2.09	35	0.66	0.38, 1.14
5	62	0.78	0.54, 1.15	0.86	0.56, 1.33	9	0.43	0.14, 1.29	51	1.00	0.62, 1.62
P-trend		0.133		0.261			0.199			0.226	
P-interaction							0.319				
ω-6 Fatty Acids											
LA (18:2ω6)											
1	53	1.00	Referent	1.00	Referent	15	1.00	Referent	38	1.00	Referent
2	46	0.94	0.62, 1.42	0.93	0.59, 1.48	15	1.30	0.55, 3.09	31	0.81	0.47, 1.41
3	59	1.10	0.74, 1.63	1.16	0.75, 1.78	11	0.94	0.37, 2.40	48	1.22	0.75, 1.99
4	54	0.87	0.58, 1.30	0.94	0.60, 1.48	11	0.80	0.31, 2.11	42	0.99	0.59, 1.65
5	65	0.92	0.62, 1.35	0.88	0.57, 1.36	10	0.53	0.19, 1.51	53	1.00	0.62, 1.63
P-trend		0.576		0.595			0.129			0.776	
P-interaction							0.134				
AA (20:4ω6)											
1	56	1.00	Referent	1.00	Referent	15	1.00	Referent	38	1.00	Referent
2	53	1.05	0.70, 1.57	1.01	0.64, 1.59	17	1.02	0.43, 2.45	31	0.99	0.58, 1.70
3	53	1.02	0.68, 1.54	1.02	0.65, 1.61	8	0.56	0.20, 1.59	48	1.17	0.70, 1.97
4	55	1.12	0.76, 1.67	1.20	0.78, 1.85	9	0.74	0.28, 1.96	42	1.32	0.81, 2.16
5	60	1.11	0.75, 1.64	1.05	0.68, 1.62	13	1.21	0.51, 2.84	53	1.01	0.61, 1.67
P-trend		0.530		0.599			0.945			0.630	
P-interaction							0.915				
Total ω-6 PUFAs (LA + AA)											
1	53	1.00	Referent	1.00	Referent	16	1.00	Referent	37	1.00	Referent
2	45	0.92	0.61, 1.40	0.92	0.58, 1.46	14	1.09	0.47, 2.56	31	0.84	0.48, 1.46
3	57	1.07	0.72, 1.58	1.13	0.73, 1.74	11	0.86	0.34, 2.13	46	1.21	0.74, 2.00
4	54	0.89	0.59, 1.33	0.95	0.60, 1.48	10	0.64	0.24, 1.69	43	1.06	0.63, 1.77
5	67	0.95	0.65, 1.40	0.92	0.60, 1.41	11	0.55	0.21, 1.48	54	1.05	0.65, 1.71
P-trend		0.756		0.747			0.121			0.613	
P-interaction							0.115				

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; BMI, body mass index; CI, confidence interval; DHA docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio; LA, linoleic acid; PUFA, polyunsaturated fatty acid.

[a] Energy-adjusted quintiles of fatty acid intake in mg/day.

[b] HRs and 95% CIs were derived from Cox proportional hazards regression models and adjusted for age (time variable), time period, and total energy intake.

[c] Additionally adjusted for US region, education, body mass index, physical activity, alcohol consumption, smoking, fruit consumption, vegetable consumption, age at menarche, age at menopause, parity, age at first birth, duration of combined hormone therapy, duration of estrogen-alone hormone therapy, duration of oral contraceptive use, and diabetes.

[d] Weight (kg)/height $(m)^2$.

[e] *P* values for trend were calculated by treating categorical exposure variables as continuous in regression models.

[f] *P* values for interaction were calculated by means of the Wald test using a cross-product term in regression models.

METHODS

Black Women's Health Study

The BWHS is an ongoing prospective cohort study of 59,001 African-American women (18). Briefly, in 1995, women between the ages 21 and 69 years enrolled in the study by completing a comprehensive self-administered baseline questionnaire, which included questions about participants' medical and reproductive histories and lifestyle and a food frequency questionnaire (FFQ). Biennial follow-up questionnaires are mailed to update exposures and medical histories and to ascertain outcomes. Women were excluded from the present analysis at the start of follow-up (1995) if they reported a positive history of uterine cancer ($n = 261$), had undergone hysterectomy ($n = 10,557$), or had an unknown menopausal status or a surgical cause of menopause ($n = 130$). Exclusions were also made for 451 additional women who only responded to the baseline questionnaire. Following exclusions, there were 47,602 women available for study. All participants provided informed consent by filling out questionnaires, and study procedures were approved by the Institutional Review Board of the Boston University Medical Center (Boston, Massachusetts).

Diet assessment

Diet was assessed in 1995 and again in 2001 using a modified version of the National Cancer Institute-Block short-form FFQ (19, 20). Data were collected on usual frequency and portion size (1995: small, medium, or large, relative to the stated medium portion size; 2001: small, medium, large, or supersize) of foods and beverages consumed during the previous 12 months. In the 1995 FFQ, women were queried on their intakes of fried fish/fish sandwiches, other fish (baked or broiled), and canned tuna fish (tuna salad or casserole). In 2001, the FFQ was expanded to include questions on participants' intakes of dark-meat fish (baked/broiled; including sardines, mackerel, and salmon) and shellfish (shrimp, crab, and lobster). Serving size-adjusted fish data were categorized into quartiles, and time-varying variables were created for baked/broiled fish (1995: other fish; 2001: dark-meat fish + other fish), fried fish, and canned tuna. A summary time-varying variable, "total fish," representing the sum of the above intakes separately in 1995 and in 2001, was also created. Category cutpoints for quartiles of total fish intake in 1995 were ≤0.6, 0.7–1.1, 1.2–2.2, and >2.2 servings/day, and in 2001 they were ≤1.0, 1.1–2.0, 2.1–3.5, and >3.5 servings/day.

Estimation of fatty acid intake

The average daily intake of specific fatty acids was calculated by multiplying the serving size-adjusted frequency of intake for each specific food by its fatty acid content, as determined by DIETCALC software, version 1.4.1 (National Cancer Institute, Rockville, Maryland). Fatty acid data were energy-adjusted using the residual method (21), categorized into quintiles, and set as time-varying. Summary variables representing total LC ω-3 PUFAs (mg/day; defined here as eicosapentaenoic acid (EPA; 20:5ω3) + docosapentaenoic acid (DPA; 22:5ω3) + docosahexaenoic acid (DHA; 22:6ω3)) and total ω-6 PUFAs (defined as linoleic acid (18:2ω6) + arachidonic acid (20:4ω6)) were also created. Energy-adjusted quintile cutpoints for total LC ω-3 PUFAs in 1995 were ≤54.9, 55.0–83.7, 83.8–117.6, 117.7–173.6, and >173.6 mg/day, and in 2001 they were ≤98.9, 99.0–148.1, 148.2–209.1, 209.2–311.8, and >311.8 mg/day.

Follow-up for cancer and censoring

Participants reported new diagnoses of "uterine cancer" on biennial follow-up questionnaires from 1997 through 2013. The 1995 and 2011 questionnaires did not ask specifically about uterine cancer but asked participants to report any "other serious illness." Cases were also identified through state cancer registry records. In total, there were 317 potential incident cases. Thirteen of these women told us they had a condition other than uterine cancer when contacted for permission to release medical records and were excluded as cases. We obtained medical records, cancer registry data, or death certificate data for 216 potential cases. Among them, 194 were confirmed as endometrial cancer, 5 were uterine sarcomas, and 17 were disconfirmed as cases by these records. Because the confirmation rate was high, we accepted the remaining 88 potential cases as cases of incident endometrial cancer. Thus, after the exclusion of the 5 sarcomas and 17 disconfirmed cases, there were a total of 282 cases of endometrial cancer (194 confirmed and 88 unconfirmed) available for study after a median follow-up of 18 years. Participants were right-censored from the analysis at the earliest date of the following occurrences: death, loss to follow-up, hysterectomy, or March 1, 2013, the end of follow-up for the present analysis.

Statistical analyses

Age and energy-adjusted least-squares mean values for total LC ω-3 PUFAs and their corresponding 95% confidence intervals were calculated within categories of participants' baseline characteristics. Distributions of LC ω-3 PUFAs are given overall and stratified on BMI.

Age- and time-period-stratified Cox proportional hazards regression models were used to estimate age- and energy-adjusted and multivariable-adjusted hazard ratios, as well as 95% confidence intervals, for the associations between fatty acid or fish consumption and endometrial cancer risk. Considered for inclusion in regression models were known or suspected endometrial cancer risk factors, selected a priori. Cox models were adjusted for age (in 1-year intervals), time period (2-year questionnaire cycle), US region of residence, education, BMI, physical activity, alcohol consumption, pack-years of smoking, fruit consumption, vegetable consumption, age at menarche, age at natural menopause, age at first birth, parity, duration of estrogen-plus-progestin hormone therapy, duration of estrogen-alone hormone therapy, duration of contraceptive use, and self-reported history of diabetes. Using indicator terms, all variables were adjusted for as they are categorized in Table 1, with the exception of BMI, which was included in regression models as a continuous variable; total energy, which was modeled as a continuous and time-varying variable; and dietary fatty acid or fish exposures, which were categorized in fifths and quarters, respectively, and time-varying. *P* values for linear trend (*P*-trend)

were calculated across categories of fatty acid intake or fish consumption by treating categorical exposure variables as continuous in regression models. All reported *P* values are 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Because previous studies have indicated that associations between LC ω-3 PUFAs or fish intake and endometrial cancer risk are modified by BMI (16, 17), we present results of all analyses both overall and stratified on BMI (<25 vs. ≥25). Regression models that stratified results on BMI adjusted for continuous BMI within strata. *P* values for interaction (*P*-interaction) were calculated using the Wald test for the inclusion of a cross-product term of the ordinal categorical exposure and the 2-category effect modifier.

RESULTS

Higher intakes of LC ω-3 PUFAs (EPA + DPA + DHA) were associated with increased age, education, physical activity, duration of oral contraceptive use, and consumption of alcohol, fruits, and vegetables (Table 1). Higher intakes of LC ω-3 PUFAs were associated with decreased BMI and parity. Premenopausal women consumed more LC ω-3 PUFAs than postmenopausal women. Most of these associations did not differ appreciably when the data were stratified on BMI (<25 vs. ≥25).

Multivariable-adjusted associations between dietary LC ω-3 PUFA intake and endometrial cancer risk, both overall and by BMI, are given in Table 2. Contrasting the highest quintiles of intake with the lowest quintiles, the hazard ratio for total dietary LC ω-3 PUFAs was 0.79 (95% confidence interval (CI): 0.51, 1.24). Endometrial cancer hazard ratios were similar for intakes of EPA (hazard ratio (HR) = 0.72), DPA (HR = 0.88), and DHA (HR = 0.84), as well as the plant-based ω-3 PUFA α-linolenic acid (HR = 0.86). Confidence intervals for each association were wide, and *P* values for trend were not statistically significant for any ω-3 fatty acid. Similarly, intakes of total or individual ω-6 PUFAs were not associated with endometrial cancer risk (linolenic acid + arachidonic acid (quintile 5 vs. quintile 1): HR = 0.92, 95% CI: 0.60, 1.41; *P*-trend = 0.75).

When the data were stratified on BMI, the hazard ratio for total and individual ω-3 PUFAs was stronger among normal-weight women (for total LC ω-3 PUFAs, HR = 0.53, 95% CI: 0.18, 1.43) than among overweight/obese women (HR = 0.88, 95% CI: 0.54, 1.43; *P*-interaction = 0.69), but these hazard ratios were not statistically different, and there were no linear trends within each BMI stratum. The hazard ratio for total ω-6 PUFA intake was 0.55 (95% CI: 0.21, 1.48; *P*-trend = 0.12) among normal-weight women and 1.05 (95% CI: 0.65, 1.71; *P*-trend = 0.61) among overweight women (*P*-interaction = 0.12).

Similarly to findings for LC ω-3 PUFAs, intakes of fish were not associated with endometrial cancer risk overall (Table 3). Upon stratification by BMI, the hazard ratio comparing the highest quartiles of total fish intake (driven primarily by baked/broiled fish) with the lowest quartiles was smaller among normal-weight women (HR = 0.65, 95% CI: 0.26, 1.61; *P*-trend = 0.79), but again confidence intervals were wide, and tests for linear trend and interaction were statistically nonsignificant.

To assess whether the more detailed assessment of fish intake on the 2001 FFQ influenced our findings, we restricted the analyses to the 2001–2013 incidence period (210 cases and 628,384 person-years). Total LC ω-3 PUFA intake and total fish intake were not associated with endometrial cancer risk overall, but hazard ratios remained smaller among women with BMI <25 (HR = 0.62 (95% CI: 0.14, 2.89) and HR = 0.79 (95% CI: 0.22, 2.80), respectively).

DISCUSSION

In this large, prospective cohort study of African-American women, dietary intakes of LC ω-3 PUFAs and fish were not associated with incidence of endometrial cancer, nor were there clear linear trends. While there was some suggestion of reduced risk among women with BMIs less than 25, there was no evidence of a dose-response association with increasing consumption of LC ω-3 PUFAs or fish, and numbers of exposed cases were small.

The primary source of dietary LC ω-3 PUFAs is oily fish (including salmon, fresh (i.e., not canned) tuna, and mackerel). LC ω-3 PUFAs are thought to reduce inflammation through several complex mechanisms, including inhibition of the nuclear factor κB gene (*NF-κB*) (22), which acts as a transcription factor for targets associated with inflammation, including the interleukin 6 gene (*IL-6*) and the cyclooxygenase 2 gene (*COX-2*). Incorporation of LC ω-3 PUFAs on cell phospholipid membranes reduces the synthesis of arachidonic acid-derived eicosanoids, including prostaglandin E_2 (22), and results in the production of prostaglandin E_3, which has less inflammatory potential (23). Lastly, LC ω-3 PUFAs modulate T-cell signaling and proliferation (22). In addition to a wealth of cell and animal experimental studies, LC ω-3 PUFAs have been shown to hold antiinflammatory properties in epidemiologic studies (11, 12) and randomized clinical trials (13–15). They are further hypothesized to have chemoprotective properties for endometrial cancer (and other estrogen-dependent cancers), as inhibition of inflammation via *NF-κB* and *COX-2* is associated with reduced estrogen synthesis (24–26), which is thought to be a critical component for endometrial proliferation (27, 28). However, this latter hypothesized mechanism predominantly represents inhibition of estrogen signaling via aromatase, which would be expected to occur primarily among noncycling (i.e., postmenopausal) women.

Researchers in 2 prospective cohort studies (16, 17) and 1 population-based case-control study (29) have reported on associations between LC ω-3 PUFAs and endometrial cancer risk in predominantly white study populations. Findings are somewhat inconsistent. Among postmenopausal women in the VITAL Study (<1% African-American), a cohort study of women living in the Seattle-Puget Sound, Washington, area, we previously reported that hazard ratios for endometrial cancer associated with intakes of LC ω-3 PUFAs were 1.66 (95% CI: 1.09, 1.55) and 1.79 (95% CI: 1.16, 1.75) for EPA and EPA + DHA, respectively (16). However, there were clear differences in the associations when the analysis was stratified on BMI. In contrast to the positive association observed among all women, LC ω-3 PUFA intakes were associated with a reduction in incidence among normal-weight women (EPA: HR = 0.42, 95% CI: 0.18, 0.99 (*P*-trend = 0.05);

Table 3. Associations Between Fish Intake and Endometrial Cancer Risk in the Black Women's Health Study, Overall and Stratified on Body Mass Index, 1995–2013

Quartile of Fish Intake[b]	No. of Cases	HR[c]	95% CI	HR[c,d]	95% CI	BMI[a] <25			BMI ≥25		
						No. of Cases	HR[c,d]	95% CI	No. of Cases	HR[c,d]	95% CI
Total fish											
1	57	1.00	Referent	1.00	Referent	12	1.00	Referent	44	1.00	Referent
2	58	0.87	0.59, 1.29	0.83	0.54, 1.26	11	0.57	0.22, 1.48	47	0.92	0.57, 1.48
3	85	1.23	0.86, 1.75	1.19	0.80, 1.76	21	1.35	0.62, 2.94	62	1.15	0.73, 1.82
4	63	0.79	0.54, 1.17	0.86	0.56, 1.31	14	0.65	0.26, 1.61	49	0.94	0.58, 1.53
P-trend[e]			0.586		0.905			0.793			0.954
P-interaction[f]								0.712			
Baked/broiled fish											
1	84	1.00	Referent	1.00	Referent	12	1.00	Referent	71	1.00	Referent
2	83	0.94	0.67, 1.30	1.05	0.73, 1.51	20	1.44	0.63, 3.27	62	0.97	0.64, 1.47
3	52	0.87	0.60, 1.25	1.11	0.74, 1.67	16	1.71	0.72, 4.02	36	0.99	0.62, 1.59
4	53	0.75	0.51, 1.08	0.88	0.58, 1.34	12	0.66	0.24, 1.84	40	0.95	0.59, 1.50
P-trend			0.112		0.638			0.566			0.840
P-interaction								0.955			
Tuna salad/casserole											
1	63	1.00	Referent	1.00	Referent	10	1.00	Referent	52	1.00	Referent
2	71	1.10	0.77, 1.58	1.04	0.71, 1.54	17	1.48	0.62, 3.52	53	0.92	0.60, 1.43
3	76	1.07	0.75, 1.52	0.93	0.63, 1.37	21	1.35	0.56, 3.23	55	0.83	0.54, 1.29
4	63	1.05	0.72, 1.54	0.93	0.61, 1.40	15	1.65	0.66, 4.06	47	0.80	0.50, 1.28
P-trend			0.858		0.584			0.355			0.294
P-interaction								0.111			
Fried fish/shellfish											
1	71	1.00	Referent	1.00	Referent	21	1.00	Referent	49	1.00	Referent
2	63	1.22	0.85, 1.74	1.22	0.82, 1.81	12	0.56	0.23, 1.36	50	1.55	0.98, 2.46
3	85	1.46	1.04, 2.04	1.45	1.00, 2.11	17	1.04	0.50, 2.18	67	1.65	1.06, 2.59
4	57	1.05	0.71, 1.55	1.08	0.70, 1.65	12	0.82	0.33, 2.05	45	1.22	0.74, 2.00
P-trend			0.745		0.436			0.915			0.350
P-interaction								0.907			

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

[a] Weight (kg)/height $(m)^2$.

[b] Quartiles of fish intake in serving-size-adjusted servings/week.

[c] HRs and 95% CIs were derived from Cox proportional hazards regression models and adjusted for age (time variable), time period, and total energy intake.

[d] Additionally adjusted for US region, education, body mass index, physical activity, alcohol consumption, smoking, fruit consumption, vegetable consumption, age at menarche, age at menopause, parity, age at first birth, duration of combined hormone therapy, duration of estrogen-alone hormone therapy, duration of oral contraceptive use, and diabetes.

[e] *P* values for trend were calculated by treating categorical exposure variables as continuous in regression models.

[f] *P* values for interaction were calculated by means of the Wald test using a cross-product term in regression models.

DHA: HR = 0.35, 95% CI: 0.14, 0.85 (*P*-trend = 0.02)). Among overweight/obese women, LC ω-3 PUFAs were associated with more than a 2-fold higher endometrial cancer risk (EPA: HR = 2.62, 95% CI: 1.55, 4.41 (*P*-trend < 0.001); DHA: HR = 2.60, 95% CI: 1.53, 4.40 (*P*-trend < 0.001)). *P* values for interactions between EPA, DHA, and EPA + DHA intake and BMI were all statistically significant.

In the largest study of this topic to date (to our knowledge), we recently examined these associations in the WHI (n = 5,745 African Americans (<7%)) (17). Relative to women who consumed the lowest amount of LC ω-3 PUFAs (EPA + DPA + DHA), women who consumed the most had a 19% reduced risk (HR = 0.81, 95% CI: 0.66, 1.00; *P*-trend = 0.04) of endometrial cancer. Associations were similar for the individual fatty acids. Upon stratification by BMI, we observed stronger reductions in endometrial cancer risk among normal-weight women, but they did not replicate the increased risk observed in the VITAL Study among overweight/obese women.

For normal-weight women, the highest quintile of LC ω-3 PUFA intake versus the lowest quintile was associated with a 41% reduction (HR = 0.59, 95% CI: 0.40, 0.86; *P*-trend = 0.001) in incidence, whereas for overweight/obese women, there was no association with risk (*P*-trend = 0.91; *P*-interaction = 0.01). In the case-control study ($n = 71$ nonwhites (<7%)), Arem et al. (29) reported 36%–43% reductions in the odds of endometrial cancer, but they did not examine effect modification by BMI. In the current study, the magnitude of associations between LC ω-3 PUFA intake and endometrial cancer risk, both overall and among normal-weight women, were similar to those reported in the WHI.

Aside from differences in race/ethnicity, there are a few other notable differences between the BWHS and prior studies. In the VITAL Study, the energy-adjusted mean LC ω-3 PUFA (i.e., EPA + DPA + DHA) intake was 193 mg/day (difference between quintile 5 and quintile 1 = 148 mg/day), and in the WHI, it was 143 mg/day (quintile 5 − quintile 1 = 196 mg/day). In the BWHS, the adjusted mean intake was 121 mg/day at baseline (1995) and 193 mg/day in 2001 (1995: quintile 5 − quintile 1 = 119 mg/day; 2001: quintile 5 − quintile 1 = 212 mg/day). The increase in LC ω-3 PUFA content between 1995 and 2001 was probably due to the use of expanded questions to ascertain fish intake on the 2001 questionnaire. Additionally, previous studies were conducted in mostly postmenopausal women ($n = 1{,}260$ premenopausal women in the VITAL Study), whereas many BWHS women were premenopausal. However, LC ω-3 PUFA intakes among postmenopausal women in the BWHS were lower than those of premenopausal women. Although different FFQs were used in the BWHS versus the VITAL and WHI studies, questions regarding fish intake, the primary source of LC ω-3 PUFAs in the diet, were nearly identical.

Hazard ratios for high intakes of α-linolenic acid (18:3ω3), linolenic acid (18:2ω6), and total ω-6 PUFAs were consistently below 1.0 among normal-weight women in the present study, although the estimates were all compatible with 1.0. Inverse associations are not supported by previous studies, which have found no associations between intakes of these fatty acids and risk of endometrial cancer (16, 17, 29).

The fact that we observed associations for LC ω-3 PUFAs similar in magnitude and direction to those of the WHI (and in some cases, the VITAL Study) suggests that our findings, while relatively imprecise, may indeed have meaning. Nevertheless, the reductions in risk we observed with high intakes of α-linolenic acid or linolenic acid in women with BMIs less than 25 complicate the interpretation of the LC ω-3 PUFA data. In previous studies, there was some evidence of an inverse association between LC ω-3 PUFA intake and risk of type I (i.e., endometrioid) endometrial cancers (16, 17). Only 60% of endometrial cancer cases in the BWHS had medical record data available for abstraction of histological subtype, leaving too few cases for subtype analysis here.

Results from several case-control studies of fish intake and endometrial cancer risk have been mixed (30). There have been 4 prospective studies of fish consumption and endometrial cancer risk (16, 17, 31, 32). Findings among them have also been inconsistent. Null results were reported for total or fried fish in the National Institutes of Health-AARP [formerly American Association of Retired Persons] Diet and Health Study ($n = 10{,}287$ nonwhites (9%)) (31), and total seafood intake was associated with a 40% increased (95% CI not given; *P*-trend < 0.05) endometrial cancer risk in the Iowa Women's Health Study ($n = 193$ African Americans (<1%)) (32). In the Iowa Women's Health Study, BMI was not included for adjustment in regression models, but it is unclear whether this would explain the study's findings. In contrast to the National Institutes of Health-AARP and Iowa Women's Health Study cohorts, and similar to the findings reported here, the highest categories of intake of baked or broiled fish (relative to the lowest categories) in the VITAL Study (16) and the WHI (17) were associated with 57% (HR = 0.43, 95% CI: 0.16, 1.13; *P*-trend = 0.12) and 46% (HR = 0.54, 95% CI: 0.34, 0.88; *P*-trend < 0.001) reductions in endometrial cancer risk, respectively, among normal-weight women. Similar to findings reported for LC ω-3 PUFA intake, increased endometrial cancer risks were observed for baked or broiled fish intake among overweight/obese women in the VITAL Study (HR = 2.87, 95% CI: 1.27, 6.51; *P*-trend < 0.001, *P*-interaction = 0.02) (16), and no associations were observed among overweight/obese women in the WHI (*P*-trend = 0.24, *P*-interaction = 0.04) (17).

This study had several notable strengths. To our knowledge, it was the first study to examine the associations between LC ω-3 PUFA consumption and endometrial cancer risk in African-American women. Unlike previous analyses that relied exclusively upon baseline diet data (16, 17), in the BWHS, dietary intake was measured over the course of 2 FFQs given 6 years apart. In this study, the intraclass correlation coefficient for correlation between total LC ω-3 PUFAs measured in 1995 and in 2001 was 0.13. This low correlation was probably due in part to the expansion of the 2001 FFQ to measure additional fish items. Nevertheless, the reliability of 2 FFQs separated by several years would be expected to be fairly low, lending added support to the inclusion of repeated measures in our regression analyses. Additionally, several important confounders were controlled.

Our study also had a number of limitations. The relatively young cohort, with a median baseline age of 35 years, resulted in small case numbers for this analysis, especially for analyses stratified on BMI, and therefore limited our statistical power to detect anything but the strongest of associations. Nevertheless, with 282 incident endometrial cancers, there were slightly more cases than in the VITAL Study cohort ($n = 263$ cases). Medical records were unavailable for 40% of incident endometrial cancers; misclassification of cases would have tended to bias associations towards the null value. Additionally, line items in the FFQ that assessed fish intake were not validated in the BWHS, thereby adding to nondifferential measurement error, which may further explain our null findings.

In summary, in the present study, results were null, with some suggestion that intakes of LC ω-3 PUFAs are associated with reduced risks of endometrial cancer among African-American women with lower body mass. These findings among leaner women support recent and similar findings from prospective studies conducted among predominantly white populations (16, 17).

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Author affiliations: Division of Cancer Prevention and Control, Department of Internal Medicine, Ohio State College

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