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Omega-3 and omega-6 fatty acid intakes and endometrial cancer risk in a population-based case–control study

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Abstract

Purpose—Animal and laboratory studies suggest that long-chain omega-3 (n-3) fatty acids, a type of polyunsaturated fat found in fatty fish, may protect against carcinogenesis, but human studies on dietary intake of polyunsaturated fats and fish with endometrial cancer risk show mixed results.

Methods—We evaluated the associations between endometrial cancer risk and intake of fatty acids and fish in a population-based sample of 556 incident cancer cases and 533 age-matched controls using multivariate unconditional logistic regression methods.

Results—Although total n-3 fatty acid intake was not associated with endometrial cancer risk, higher intakes of eicosapentaenoic (EPA 20:5) and docosahexaenoic (DHA 22:6) fatty acids were significantly associated with lower risks (OR = 0.57, 95 % CI: 0.39–0.84; OR = 0.64, 95 % CI: 0.44–0.94; respectively) comparing extreme quartiles. The ratio of n-3:n-6 fatty acids was inversely associated with risk only on a continuous scale (OR = 0.84, 95 % CI: 0.71–0.99), while

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total fish intake was not associated with risk. Fish oil supplement use was significantly associated with reduced risk of endometrial cancer: OR = 0.63 (95 % CI: 0.45–0.88).

Conclusions—Our results suggest that dietary intake of the long-chain polyunsaturated fatty acids EPA and DHA in foods and supplements may have protective associations against the development of endometrial cancer.

Keywords

Endometrial cancer; Fatty acids; Fish oil; Fish; Case–control study

Introduction

It is estimated that in the United States, 47,000 women will be diagnosed with endometrial (uterine corpus) cancer in 2012, making it the 4th most commonly occurring cancer among women [1]. Many known risk factors for the disease are hormone-related such as postmenopausal hormone replacement, ovarian dysfunction, infertility, and tamoxifen use; protective factors include higher parity and oral contraceptive use [2, 3]. Other risk factors include obesity, type II diabetes and low physical activity [4, 5]. Previous publications show that parity, oral contraception, body mass index (BMI), physical activity and diet may explain up to 80 % of the risk of endometrial cancer, emphasizing the importance of lifestyle modification for prevention of this disease [6].

Laboratory and animal studies have shown that long-chain omega-3 (n-3) polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6), inhibit tumorigenesis for various cancer sites [7–10]. Omega-6 PUFAs such as arachidonic acid (20:4), on the other hand, have been shown to promote tumor growth [11] and have pro-inflammatory effects in rats [12]. Given their opposing effects, the ratio of n-3 to n-6 PUFAs has long been hypothesized to be important in carcinogenesis [12, 13].

Epidemiological evidence on the association of n-3 fatty acid intake with endometrial cancer risk is limited. The major dietary source of long-chain n-3 fatty acid intake, fatty fish, has been evaluated in relation to cancer outcomes in studies that do not otherwise isolate individual fatty acids. Of two relevant cohort studies, one reported an increased risk of endometrial cancer associated with consumption of fish and processed meat together, but did not separate fish consumption or assess an association with polyunsaturated dietary fat [14]. The other cohort study showed no association between polyunsaturated fat, total n-3 fatty acids, and endometrial cancer risk, but did not analyze fish intake [15]. Seven case–control studies [16–21] and a case–cohort study [22] found no association between total fish intake and endometrial cancer, while two case–control studies, both from China, reported an increased risk associated with higher freshwater fish consumption [23, 24] and another suggested an inverse association between consumption of fatty fish (typically found in marine, saltwater environments) and endometrial cancer risk [25]. Multiple case–control studies [16, 19, 26, 27] and one cohort study [15] reported no association between polyunsaturated fat intake and endometrial cancer risk but did not separately analyze n-3 or n-6 fatty acids.

Although the published literature suggests no association between total polyunsaturated fat intake and endometrial cancer, no previous study, to our knowledge, has comprehensively examined intake of individual n-3 and n-6 fatty acids, the n-3:n-6 ratio, and intake from supplements and food sources in relation to endometrial cancer risk. The principal aim of this study was to examine the independent associations of these fatty acid sources with endometrial cancer risk.

Materials and methods

Study design

A population-based case–control study was conducted in Connecticut, involving English-speaking residents aged 35–81 years who were diagnosed with incident, primary endometrial cancer between October 2004 and September 2008. Study design and eligibility have been described elsewhere [5]. Of the 1,216 potentially eligible patients identified statewide through the Rapid Case Ascertainment Shared Resource of the Yale Cancer Center, 317 chose not to participate, 19 had died before study contact, 13 were too ill, 44 could not be located, 68 could not be reached by telephone and 87 were ineligible. Among 1,995 Connecticut women in the eligible age range identified as potential controls through random digit dialing, 1,447 agreed to further contact for participation and 1,248 were contacted, while 111 were ineligible due to residence, mental impairment, language barrier, cancer diagnosis or ineligible medical conditions. Another 92 women were disqualified due to illness or residence outside of Connecticut, and 371 refused to participate. Research staff enrolled 668 (54.9 %) of diagnosed endometrial cancer cases and 674 (64.5 %) of contacted, eligible controls. In person interviews were carried out at participant homes. After completion of signed informed consent, study staff administered structured questionnaires on ethnic and demographic factors, environmental exposures and lifestyle factors. The study was approved by the Institutional Review Boards of Yale University, the Connecticut Department of Public Health Human Investigation Committee and the 28 participating Connecticut hospitals.

Exposure assessment

Diet was assessed using a self-administered 120-item food frequency questionnaire (FFQ) from the Fred Hutchinson Cancer Research Center. This FFQ was modified from the Women's Health Initiative FFQ, and was validated against 4-day food records and 24-h dietary recalls with published measurement characteristics [28]. Participants completed the mailed questionnaire, which was reviewed by research staff during the home visit. The FFQ inquired about the frequency and portion size of various foods based on estimated usual intake over the previous 1–5 years and >19 adjustment questions queried about types and quantities of fat used in cooking and at the table. These responses were applied to analysis algorithms to normalize calculated fat intakes. Participants were specifically asked about consumption of dark fish (such as salmon, mackerel or blue-fish), white fish (such as sole, halibut, snapper or cod), shellfish (such as shrimp, lobster, crab or oysters) and fried fish on separate line items. Also, they were asked whether they took fish oil, omega-3 or cod liver oil in the 1–5 years prior and if so, they were asked to choose a category for frequency of supplementation (<1/week, 1–2 days/week, 3–4 days/week, 5–6 days/week, 7 days/week). The primary nutrient density database for this FFQ was derived from the Nutrition Data Systems for Research (NDS-R, version 2008, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) and has been augmented with information from manufacturers. Cases were asked to recall average diet in the period 1–5 years prior to diagnosis so as to minimize dietary changes occurring because of disease; controls were asked to recall average diet 1–5 years prior to interview.

Statistical analysis

Control women who had a hysterectomy ($n = 6$) or were outside the specified age range ($n = 3$) were excluded from analyses. We excluded study subjects who missed >10 items on the FFQ ($n = 118$ cases and 89 controls) as these FFQs were considered unreliable. We also removed subjects whose calculated energy intake was less than 600 ($n = 28$) or above 5,000 kcal per day ($n = 9$) on the FFQs as these cutoffs have been used in similar populations to eliminate subjects whose FFQ information is believed to be inaccurate or unrepresentative

of usual diet [29, 30]. Our final analytic sample size was 556 cases and 533 controls. We performed descriptive analyses using the t-distribution for continuous variables and Chi-squared distribution for categorical variables. Total n-6 fatty acids included linoleic acid (18:2) and arachidonic acid (20:4). n-3 fatty acids were summed as the total of linolenic acid (18:3), eicosapentaenoic acid (EPA, 20:5) docosahexaenoic acid (DHA, 22:6), and docosapentaenoic acid (22:5). Individual fatty acids were divided into quartiles based on intake among controls. Total fish consumption was calculated as the sum of reported fried, dark, white and shellfish weekly servings. Because fish consumption in our study population was low for specific types of fish, we analyzed fried, dark, white and shellfish individually into categories of ever (>0 servings/year) or never (0 servings/year).

We examined the correlation between individual and grouped fatty acids and report selected Spearman correlation coefficients as follows: total n-6 PUFAs and linoleic acid = 0.99, DHA and EPA = 0.95, docosapentaenoic acid and DHA = 0.91, docosapentaenoic acid and EPA = 0.95. Given the high correlations between docosapentaenoic acid and the long-chain fatty acids DHA and EPA, very low absolute intake of docosapentaenoic acid and an insufficient body of evidence supporting a role for docosapentaenoic acid in carcinogenesis, docosapentaenoic acid was not analyzed for its main effect, but rather included in total n-3 fatty acids.

To account for differences in fatty acid intake due to differences in total energy we used the multivariate nutrient density method, dividing fatty acid intake by total energy and multiplying by 1,000 [31]. After assessing differences in quartiles using the log rank test, to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) we built logistic regression models. All variables in Table 1 were examined for possible confounding. We retained variables significant at the two-sided $p = 0.05$ level, those that caused a>10 % change in odds ratio estimates and variables that were selected a priori to be included in the model based on previously observed associations with risk. For final statistical models, we included adjustment for age at interview (continuous), race (white or other), body mass index (continuous), number of live births (continuous), menopausal status (yes/no), oral contraceptive use (ever/never), smoking category (never, former, current), and physician-diagnosed hypertension (yes/no). Education, diabetes, vegetable consumption and physical activity levels were considered but were not included in the multivariate-adjusted models because adding these variables to the models did not change parameter estimates by >10 %. We performed linear trend tests by assigning values of 1–4 for each quartile and treating the ordinal variable as continuous. To maximize power, we also created continuous models scaling the exposure of interest by the interquartile range.

Results

Characteristics of cases and controls are shown in Table 1. On average, cases reported higher baseline BMI ($p < 0.001$), less physical activity in the past 2–5 years ($p < 0.001$), higher frequency of physician-diagnosed hypertension ($p < 0.001$) and diabetes ($p = 0.002$), and were more likely to be post-menopausal ($p = 0.039$) and report a family history of endometrial cancer ($p = 0.026$) than controls. Compared with controls, a lower percentage of cases completed 12 or more years of education ($p = 0.015$), drank alcohol ($p < 0.001$) or used hormone therapy ($p = 0.003$). Fewer cases reported ever being pregnant ($p < 0.001$); cases also reported fewer live births ($p < 0.001$) and younger age at first pregnancy ($p < 0.001$).

Absolute intakes of individual n-3 and n-6 fatty acids are shown in Table 2. Cases reported lower intake of long-chain n-3 fatty acids EPA and DHA compared with controls ($p = 0.022$ and $p = 0.005$, respectively). Absolute intakes of these long-chain fatty acids were a small

percentage of total n-3 fatty acid intake, which was dominated by linolenic acid. Linoleic acid accounted for most of the absolute intake for total n-6 fatty acids, with arachidonic acid contributing only a small fraction of total intake.

Total n-3 and n-6 fatty acids were not associated with risk of endometrial cancer comparing the highest to lowest quartiles (Table 3). Of the n-6 fatty acids, neither linoleic acid nor arachidonic acid intakes were associated with endometrial cancer risk comparing extreme intake quartiles. Of the n-3 fatty acids, higher intakes of the long-chain marine fatty acids EPA and DHA were associated with a reduced risk of endometrial cancer. After adjusting for confounding factors, EPA showed an inverse association with endometrial cancer risk, with an OR = 0.57 (95 % CI: 0.39–0.84) comparing the highest quartile of intake to the lowest. Intake of DHA was also associated with a reduced risk of endometrial cancer comparing extreme quartiles (OR = 0.64, 95 % CI: 0.44–0.94). Because of the wide range of ages at diagnosis we stratified by median age at diagnosis (61.3 years), and observed a stronger, statistically significant association for EPA and DHA for older women and an attenuated, non-significant association for younger women (data not shown). There was no association between the ratio of n-3:n-6 fatty acids when comparing quartiles, but on a continuous scale a nominally significant protective association was observed (OR = 0.84, 95 % CI: 0.71–0.99).

As fish is a major contributor to dietary intakes of long-chain n-3 fatty acids, we also examined the association between fish consumption and the risk of endometrial cancer (Table 4). There was a suggested, but not significant, inverse association between fish intake and endometrial cancer risk (OR = 0.74, 95 % CI: 0.50–1.10). Although also not statistically significant, higher fried fish consumption appeared to be associated with increased endometrial cancer, while dark fish consumption was non-significantly inversely associated with risk. Shellfish and white fish consumption were not associated with risk.

Of the 1,089 women in this study, 85 cases (15.34 %) and 126 controls (23.64 %) reported use of fish oil, n-3, or cod liver oil supplements. Women who consumed fish oil supplements had a lower BMI, reported higher physical activity levels, lower polyunsaturated fat intake and were more likely to have used hormone therapy and been pregnant. Women who reported supplemental fish oil intake had a reduced risk of endometrial cancer (OR = 0.63, 95 % CI: 0.45–0.88) compared with women who reported no supplement use (Table 5). Adding EPA or DHA intake from food to the model yielded similar results (data not shown). To determine whether the association with supplementation differed by EPA or DHA intake, we performed analyses of fish oil supplementation stratified by dietary intake, using the energy adjusted median among controls as the cutpoint. The inverse association between fish oil supplement use and endometrial cancer was most pronounced among women consuming less than or equal to the median DHA intake (OR = 0.52, 95 % CI: 0.31–0.87). For women consuming greater than the median intake of DHA, the OR for supplemental fish oil use was 0.74 (95 % CI 0.47–1.16). For those consuming less than the median EPA intake, the OR for supplement use was 0.60 (95 % CI: 0.36–0.98), as compared with 0.67 (95 % CI: 0.43–1.06) for women consuming greater than the median EPA intake.

Discussion

In this population-based case–control study, we observed an association between higher intake of the n-3 fatty acids EPA and DHA and a reduced risk of endometrial cancer. No association was observed for total n-3 fatty acid intake, likely because EPA and DHA comprised only a small fraction of the total n-3 fatty acid intake. Total n-6 fatty acid intake and individual n-6 fatty acid intakes were not associated with endometrial cancer incidence

in our study population, while higher fish intake, particularly for dark fish, appeared to be protective. We also observed inverse associations for fish oil supplement use and the ratio of n-3:n-6 fatty acids (on a continuous scale) with endometrial cancer. Fish oil supplement use was associated with a lower risk particularly among those who reported less than the median EPA or DHA intake.

Studies on polyunsaturated fats and endometrial cancer risk show mixed results, and most studies of diet and endometrial cancer assess fat subcategories without examining individual fatty acids. Evidence from cohort studies on polyunsaturated fats and risk of endometrial cancer is limited, and to our review, do not evaluate n-3 fatty acids [15, 32]. Both hospital-based [26] and population-based [16, 33] case–control studies showed no association for polyunsaturated fat, but case numbers were low and they did not comprehensively evaluate n-3 individual fatty acids (DHA and EPA were not examined). A multiethnic population-based case–control study in Hawaii reported an increased risk of endometrial cancer with higher total poly-unsaturated fat consumption (OR = 1.5 comparing extreme quartiles, 95 % CI: not reported).

Although for individuals who consume fish, intake of long-chain n-3 fatty acids is well captured by fish intake, some studies show that up to 20 % of long-chain n-3 fatty acid intake comes from meat [34]. The 18 carbon linolenic acid (a precursor to EPA) is found in cereal-based products, meats, dark green leafy vegetables, canola oil, flaxseed, nuts, and soybeans; however, conversion of medium chain linolenic acid to longer chain fatty acids is inefficient in the human body [35]. For individuals who do not consume fish, DHA intake largely comes from eggs and meat sources. Thus, studies looking exclusively at fish capture much but not all of the intake of long-chain n-3 fatty acids. Although we did not observe a statistically significant association between total weekly fish intake and endometrial cancer risk, there was a suggested inverse association, particularly for dark fish consumption.

While few cohort studies report on fish intake and endometrial cancer risk, the Iowa Women's Health study showed an increased risk with all seafood intake (RR = 1.4, 95 % CI: not reported) and with a combined measure of fish and processed meat (RR = 1.5, 95 % CI: not reported [14]). The authors did not describe foods included in each of these categories and also did not adjust for BMI, which may attenuate the observed RR. A random effects meta-analysis of seven case–control studies showed no association between fish intake and endometrial cancer risk (OR = 1.04, 95 % CI: 0.55–1.98) but did not separate types of fish and reported high study heterogeneity [36]. After excluding three studies that did not adjust for energy the OR = 1.88 (95 % CI: 1.20–2.98). Two of the included studies [23, 24] were from China, where median consumption levels of fish (approximately 3 servings per week) were much higher than levels consumed in our study population (approximately 1 serving per week). In China, fish is often consumed as salted, dried fish containing N-nitrosamines, which are known carcinogens, or prepared using deep frying methods, which may lead to formation of mutagens and carcinogens. Although a study on animal food intake and preparation methods in the Chinese population showed no association for cooking methods and doneness levels for fish in relation to endometrial cancer risk [23], salted, dried fish were not analyzed separately. Also, while both China-based studies reported on educational achievement and adjusted where necessary, it is possible that there is residual confounding by socio-economic status comparing women who consume fish and women who do not. In contrast to (and not included in) the pooled findings, a Swedish population-based case–control study showed a protective association with higher fatty fish intake, reporting an odds ratio of 0.6 (95 % CI: 0.5–0.8) comparing those who consumed 2.0 servings per week (highest quartile median) to those who consumed 0.2 servings per week (lowest quartile median) [25], and a population-based case–control study in the United States showed a OR = 0.7 (95 % CI: 0.4–1.1) [16]. Four additional hospital-based case–control studies in Greece,

Japan, and Italy and an analysis combining hospital-based cases in northern Italy and population-based cases in Switzerland showed no associations between fish consumption and endometrial cancer risk [17, 18, 20, 21, 26].

Few epidemiologic studies have reported on fish oil supplement use and cancer incidence, but experimental evidence suggests that long-chain n-3 fatty acids may be protective against cancers such as the colon and breast [37]. Also, experimental studies in animals show that high fish oil supplementation inhibits tumor growth in chemo-induced, transplanted, or spontaneous mammary tumor models and reduces metastases occurrence [38].

Recent reviews have highlighted mechanisms by which n-3 fatty acids may be involved in cancer prevention [12, 39]. First, EPA is thought to inhibit the pro-inflammatory arachidonic acid-derived eicosanoid biosynthesis [40, 41], which modulates inflammatory and immune responses. Second, EPA and DHA have been shown to influence transcription factor activity, gene expression and signal transduction [42]. Third, high EPA intake may increase production of prostaglandin E_3 and decrease production of prostaglandin E_2, thus decreasing estrogen production and associated cell growth [43]. Fourth, studies suggest that n-3 fatty acid intake decreases superoxide production, suppressing inflammation and in turn the overproduction of free radicals and carcinogenesis [44]. Lastly, studies in rats [45, 46] and in patients with type 2-diabetes [47] suggest that n-3 PUFAs may impact insulin sensitivity and cell membrane fluidity, protecting against carcinogenesis.

Strengths of our study include a greater number of cases than in previous case–control studies of endometrial cancer, comprehensive information collected on various measures of n-3 fatty acid consumption via 120 items on the FFQ, including fish, and a separate question on fish oil consumption, allowing us to assess n-3 fatty acid intake using multiple approaches. All questionnaires were reviewed in person with participants by interviewers, affording better quality control and the potential to review accuracy of information. An established limitation of the case–control design is that lifestyle factors may be subject to recall bias. For the FFQ, we queried on consumption during the 1–5 years before diagnosis among cases to lessen the potential effect of latent disease on diet. Recently published studies measuring n-3 and n-6 fatty acid content of fish commonly consumed in the United States show considerable variability in n-3 fatty acid levels and in the ratio of n-3:n-6 fatty acids, explaining that geographic location, fish diet, seasonal variations, and environmental factors such as temperature, salinity, and the depth of the general marine habitat affect marine fat composition [12, 48]. Thus, imprecision in nutrient databases likely leads to some measurement error, whereby fish intake does not translate into accurate estimates of long-chain n-3 PUFA consumption. Also, types and farming conditions of commonly consumed fish in China may differ from fish consumed in Europe or in the United States, creating difficulties in comparing health effects of fish consumption across populations. Our evaluation of fish was limited by relatively low consumption levels and lack of range of intake for specific fish types, allowing only a comparison of ever versus never consumption. In addition, while we had information on frequency of fish oil supplement use, we did not have power to more finely assess the association of frequency of supplement use with endometrial cancer risk because nearly all women who took supplements reported daily consumption. We did not have information on supplemental EPA and DHA doses and thus could not calculate total EPA or DHA from both supplemental and dietary intakes. Finally, ninety-three percent of our study population was non-Hispanic white and conclusions and inferences may be more relevant for this population.

In conclusion, our study suggests an inverse association between long-chain dietary n-3 fatty acids EPA and DHA and fish oil supplement use with risk of endometrial cancer. Medium chain n-3 linolenic acid was not associated with risk, suggesting that shorter and longer

chain n-3 fatty acids may play different roles in endometrial cancer carcino-genesis. Future studies should further explore associations with intake of specific fatty acids, food sources, and blood and tissue biomarkers to understand better the associations between these fatty acids and endometrial cancer risk.

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Table 1

Description of the sample by case–control status

	Cases (*N* = 556)	Controls (*N* = 533)	*P*[c]
Demographic and lifestyle factors			
Age[a]	60.80 (9.39)	61.76 (10.93)	0.122[d]
Race[b]			0.222
White	514 (92.45)	503 (94.37)	
Other	42 (7.55)	29 (5.44)	
Education[b]			0.015
≤12 years	187 (33.63)	143 (26.83)	
>12 years	369 (66.37)	390 (73.17)	
Body mass index (kg/m^2)[a]	32.33 (8.51)	27.15 (6.26)	<0.001
Smoking status[b]			0.080
Never smoker	308 (55.40)	262 (49.16)	
Ever smoker	248 (44.60)	271 (50.84)	
Ever drank alcohol regularly[b]	264 (47.74)	312 (58.54)	<0.001
Physical activity hours per week[a]	5.48 (10.69)	8.41 (12.54)	<0.001
Sit hours per week[a]	39.14 (20.32)	44.93 (20.54)	<0.001
Calories per day[a]	1,749 (720)	1,690 (637)	0.149
Polyunsaturated fat (g/day)[a]	14.31 (9.39)	13.71 (7.25)	0.177
Reported fish oil supplement usage (ever)[b]	85 (15.34)	126 (23.64)	0.001
Reproductive factors			
Number of live births[a]	1.79 (1.36)	2.19 (1.30)	<0.001
Ever Gravid[b]	439 (78.96)	474 (88.93)	<0.001
Age at first pregnancy[a]	23.56 (4.73)	24.73 (4.91)	<0.001
Menopausal status[b]			0.039
Premenopausal	75 (13.49)	100 (18.76)	
Postmenopausal	480 (86.33)	433 (81.24)	
Oral contraceptive use (ever)[b]	323 (58.09)	345 (64.73)	0.079
Menopausal hormone use among postmenopausal women (ever)[b]	149 (31.04)	181 (41.80.71)	0.003
Menarche age[b]			0.108
<12 years	151 (27.16)	116 (21.76)	
≥12 years	401 (72.12)	414 (77.67)	
Medical history			
Family history (yes/no 1st degree relative with endometrial cancer)[b]	39 (7.01)	21 (3.94)	0.026
MD diagnosis of hypertension (ever)[b]	312 (56.12)	198 (37.36)	<0.001
MD diagnosis of diabetes (ever)[b]	108 (19.42)	66 (12.38)	0.002

[a]Table values are mean (SD) for continuous variables

[b] Table values are n (column %) for categorical variables

[c] *P* value is for *t* test (continuous variables) or χ^2 test (categorical variables)

[d] Matched by design

Table 2

Individual fatty acid intake (grams) by case–control status

	Cases (*N* = 556)	Controls (*N* = 533)	*P* value[a]
Total n-6 fatty acids	12.67 (6.62)	12.09 (6.56)	0.105
Linoleic, 18:2	12.56 (6.58)	11.97 (6.52)	0.102
Arachidonic, 20:4	0.12 (0.07)	0.12 (0.08)	0.906
Total n-3 fatty acids	1.57 (0.81)	1.55 (0.81)	0.790
Linolenic, 18:3	1.36 (0.72)	1.30 (0.68)	0.075
Eicosapentaenoic, 20:5	0.06 (0.06)	0.07 (0.10)	0.022
Docosapentaenoic, 22:5	0.02 (0.02)	0.03 (0.04)	0.022
Docosahexaenoic, 22:6	0.12 (0.15)	0.15 (0.24)	0.005

Table values are mean (SD)

[a] *P* values calculated using the Wilcoxon rank sum test

Table 3

Energy and multivariate-adjusted odds ratios[a] and 95 % confidence intervals for n-3 and n-6 fatty acids and risk of endometrial cancer

Dietary variable[b]	Quartile I	Quartile II	Quartile III	Quartile IV	P_{trend}	Continuous[c]
n-6 Polyunsaturated fatty acids, total						
N (cases/controls)	104/134	170/133	135/133	147/133		
Energy- and age-adjusted OR (95 % CI)	1.00	1.61 (1.14–2.26)	1.26 (0.89–1.80)	1.36 (0.96–1.94)	0.298	1.09 (0.94–1.28)
Multivariate-adjusted OR (95 % CI)	1.00	1.52 (1.05–2.21)	1.15 (0.78–1.69)	1.28 (0.87–1.89)	0.577	1.06 (0.89–1.26)
Linoleic acid, 18:2						
N (cases/controls)	105/134	167/133	138/132	146/134		
Energy- and age-adjusted OR (95 % CI)	1.00	1.56 (1.11–2.20)	1.29 (0.91–1.83)	1.33 (0.94–1.89)	0.312	1.10 (0.94–1.28)
Multivariate-adjusted OR (95 % CI)	1.00	1.47 (1.01–2.13)	1.17 (0.80–1.71)	1.24 (0.85–1.83)	0.592	1.07 (0.90–1.27)
Arachidonic acid, 20:4						
N (cases/controls)	139/133	162/133	131/133	124/133		
Energy- and age-adjusted OR (95 % CI)	1.00	1.14 (0.82–1.59)	0.93 (0.66–1.31)	0.89 (0.63–1.25)	0.315	0.93 (0.81–1.06)
Multivariate-adjusted OR (95 % CI)	1.00	1.05 (0.73–1.51)	0.76 (0.53–1.11)	0.74 (0.51–1.07)	0.040	0.87 (0.75–1.02)
n-3 Polyunsaturated fatty acids, total						
N (cases/controls)	155/133	130/133	147/134	124/133		
Energy- and age-adjusted OR (95 % CI)	1.00	0.83 (0.59–1.17)	0.94 (0.67–1.31)	0.80 (0.57–1.12)	0.317	0.93 (0.81–1.08)
Multivariate-adjusted OR (95 % CI)	1.00	0.79 (0.55–1.13)	1.02 (0.71–1.46)	0.75 (0.52–1.09)	0.324	0.92 (0.79–1.08)
Linolenic acid, 18:3						
N (cases/controls)	129/133	139/134	148/132	133/133		
Energy- and age-adjusted OR (95 % CI)	1.00	1.10 (0.78–1.54)	1.13 (0.81–1.59)	1.01 (0.72–1.42)	0.911	1.06 (0.90–1.24)
Multivariate-adjusted OR (95 % CI)	1.00	1.01 (0.70–1.46)	1.08 (0.75–1.56)	0. 91 (0.63–1.32)	0.733	1.02 (0.86–1.21)
Eicosapentaenoic acid, 20:5						
N (cases/controls)	161/134	148/132	163/133	84/134		
Energy- and age-adjusted OR (95 % CI)	1.00	0.94 (0.67–1.30)	1.04 (0.75–1.45)	0.54 (0.38–0.77)	0.006	0.78 (0.67–0.91)
Multivariate-adjusted OR (95 % CI)	1.00	0.81 (0.57–1.16)	0.98 (0.69–1.40)	0.57 (0.39–0.84)	0.026	0.80 (0.67–0.95)
Docosahexaenoic acid, 22:6						
N (cases/controls)	170/133	139/134	150/132	97/134		
Energy- and age-adjusted OR (95 % CI)	1.00	0.81 (0.58–1.13)	0.91 (0.66–1.26)	0.59 (0.41–0.83)	0.010	0.83 (0.72–0.96)
Multivariate-adjusted OR (95 % CI)	1.00	0.80 (0.56–1.15)	0.83 (0.58–1.19)	0.64 (0.44–0.94)	0.036	0.85 (0.73–0.997)

Dietary variable[b]	Quartile I	Quartile II	Quartile III	Quartile IV	P_{trend}	Continuous[c]
Ratio of n-3 to n-6 fatty acids						
N (cases/controls)	142/133	172/134	142/132	100/134		
Energy- and age-adjusted OR (95 % CI)	1.00	1.23 (0.89–1.71)	1.04 (0.74–1.46)	0.74 (0.52–1.05)	0.069	0.81 (0.70–0.95)
Multivariate-adjusted OR (95 % CI)	1.00	1.15 (0.81–1.65)	0.99 (0.69–1.44)	0.79 (0.53–1.17)	0.180	0.84 (0.71–0.99)

[a] Multivariate models were adjusted for energy consumption (continuous), age (continuous), body mass index (continuous), number of live births (continuous), menopausal status (pre/post), oral contraceptive use (ever/never), hypertension (yes/no), smoking status (never/former/current), and race/ethnicity

[b] Quartiles were divided based on quartiles of intake among controls

[c] Continuous model scaled by the interquartile range

Table 4

Energy- and multivariate-adjusted[a] odds ratios (OR) and 95 % confidence intervals (CI) for fish intake and risk of endometrial cancer

Total fish, servings/week[b]	**0–<0.46**	**0.46–<1.04**	**1.04–<2.00**	**≥2.00**	**P_{trend}**	**Continuous**
N (cases/controls)	147/127	147/136	147/131	115/139		
Energy- and age–adjusted OR	Ref.	0.93 (0.66–1.30)	0.95 (0.67–1.33)	0.68 (0.48–0.97)	0.050	0.92 (0.86–1.02)
Multivariate-adjusted[a] OR	Ref.	1.05 (0.73–1.52)	1.00 (0.69–1.45)	0.74 (0.50–1.10)	0.142	0.93 (0.86–1.02)

	White Fish		**Dark fish**		**Shell fish**		**Fried fish**	
	N (cases/controls)	**OR (95 % CI)[a]**	**N (cases/controls)**	**OR (95 % CI)[a]**	**N (cases/controls)**	**OR (95 % CI)[a]**	**N (cases/controls)**	**OR (95 % CI)[a]**
Never	189/153	Ref.	293/236	Ref.	278/251	Ref.	319/345	Ref.
Ever	367/380	0.88 (0.66–1.17)	263/297	0.82 (0.63–1.07)	278/282	0.91 (0.70–1.18)	237/188	1.26 (0.96–1.66)

[a]Multivariate models were adjusted for energy consumption (continuous), age (continuous), body mass index (continuous), number of live births (continuous), menopausal status (pre/post), oral contraceptive use (ever/never), hypertension (yes/no), smoking status (never/former/current), and race/ethnicity

[b]Quartiles were divided based on quartiles of intake among controls

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Table 5

Multivariate-adjusted odds ratios (OR) and 95 % confidence intervals (CI) for fish oil supplementation (ever use reported 1–5 years prior to diagnosis/interview) and risk of endometrial cancer, stratified by energy adjusted median EPA and DHA intakes from food

Supplement usage	**No**	**Yes**
N (cases/controls)	469/407	85/126
Multivariate-adjusted OR (95 % CI)[a]	Ref.	0.63 (0.45–0.88)
Supplement usage stratified by median nutrient intake		Multivariate-adjusted ORs (95 % CI)
EPA ≤ median intake[b]	Ref.	0.60 (0.36–0.98)
EPA > median intake	Ref.	0.67 (0.43–1.06)
DHA ≤ median intake[b]	Ref.	0.52 (0.31–0.87)
DHA > median intake	Ref.	0.74 (0.47–1.16)

[a]Multivariate models were adjusted for total calories (continuous), age (continuous), body mass index (continuous), number of live births (continuous), menopausal status (pre/post), oral contraceptive use (ever/never), hypertension (yes/no), smoking status (never/former/current), and race/ethnicity

[b]Median energy adjusted intake (g/1,000 kcal) among controls: EPA = 0.029; DHA = 0.057