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Polyunsaturated fatty acid interactions and breast cancer incidence: a population-based case-control study on Long Island, New York

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Abstract

Purpose—Experimental studies demonstrate that ω-3 polyunsaturated fatty acids (PUFAs) inhibit inflammatory eicosanoids generated by ω-6 PUFAs. Epidemiologic studies on dietary ω-3 PUFA intake show consistent inverse associations with breast cancer incidence among Asian populations, where ω-3, relative to ω-6, intake is high. In contrast, associations are inconsistent among Western populations, where intake of ω-3, relative to ω-6, intake is low. We hypothesized that examining interactions between ω-3 and ω-6 would help elucidate the PUFA-breast cancer association in the U.S.

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Methods—In a Long Island, NY, population-based study of 1463 breast cancer cases and 1500 controls, we estimated multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression to examine interactions between ω-3 and ω-6 intake.

Results—We observed a super-additive interaction (Relative Excess Risk Due to Interaction=0.41; 95%CI=0.06,0.76) between ω-3 and ω-6 intake in association with breast cancer incidence, although the CIs for the joint exposure of low ω-3/high ω-6 compared to high ω-3/low ω-6 intake were wide (OR=1.20; 95%CI=0.85,1.69).

Conclusions—Breast cancer risk reduction may be possible for U.S. women with dietary consumption of higher ω-3, which have anti-inflammatory properties, in concert with lower ω-6, which induce inflammation. Replication from future U.S.-based investigations is needed.

Keywords

polyunsaturated fatty acids; seafood; breast neoplasms

Introduction

Breast cancer incidence rates are more than two times higher in the United States (U.S.) and European countries than in China or Japan [1,2]. Migration studies conducted among Asian immigrants show that breast cancer incidence patterns begin to reach those of Western countries a few generations after migration [3–6], suggesting environmental factors may play a role in the geographic variation in incidence rates observed in Asian and Western countries.

One potential environmental exposure is polyunsaturated fatty acids (PUFAs), which includes two primary classes, ω-3 and ω-6 fatty acids. Laboratory studies show that ω-3 PUFAs competitively inhibit ω-6 fatty acids, thus lowering levels of inflammatory eicosanoids generated from ω-6 metabolism [7], and that higher ω-3 relative to ω-6 could reduce breast cancer through inflammation, oxidative stress, and estrogen metabolism [7–10]. Asian populations have a substantially higher ratio of ω-3/ω-6 intake compared to European and U.S. populations [11,12], due to higher fish consumption [13–15], which may partially explain the lower breast cancer risk observed in these populations [16–19]. However, previous U.S. and European epidemiologic studies examining the PUFA and breast cancer association remain inconsistent [20–40]. The biologic influence of PUFAs is unlikely to differ across populations; however, low fish intake and high ω-6 intake [41] in Western countries may mask important risk reductions. We hypothesized that consideration of both ω-3 and ω-6 intake, as an interaction or as the relative balance (ω-3/ω-6 ratio), may elucidate the potential benefit of ω-3 intake among populations with low fish consumption.

In the study reported here, we examined the interaction between dietary ω-3 and ω-6 PUFA classes in association with breast cancer risk among women on Long Island, New York (NY).

Materials and Methods

We used the population-based case-control component of the Long Island Breast Cancer Study Project (LIBCSP) comprising English-speaking residents of Nassau and Suffolk counties. Details of the LIBCSP have been published previously [42]. Institutional Review Board approval was obtained from all participating institutions.

Study population

Cases were women newly diagnosed with a first primary *in situ* or invasive breast cancer, identified using a "super-rapid" network by contacting hospital pathology departments daily or 2-3 per week. Controls were identified using Waksberg's method of random digit dialing [43] for women under 65 years of age, and Health Care Finance Administration rosters for women 65 years and older. Controls were frequency matched to the expected age-distribution of cases. There were no age or race restrictions for subject eligibility.

The parent LIBCSP respondents included 1,508 cases and 1,556 controls (82% and 63% response rates, respectively). Respondents ranged in age from 20 to 98 years of age, 67% were postmenopausal, and the majority self-reported their race as white (94%), followed by black or African American (4%), or other (2%), which is consistent with the racial distribution of these two counties at the time of data collection [44]. Most LIBCSP participants were highly educated (>90% graduating from high school), used alcohol (62%), were parous (88%), never used hormone replacement therapy (74%), never used oral contraceptives (55%), and did not have a family history of breast cancer (84%). Among cases, the majority (84%) were diagnosed with first, primary invasive breast cancer [42].

Assessment of PUFAs and other covariates

LIBCSP participants were administered a main risk factor questionnaire by a trained interviewer about 3 months after diagnosis for cases and 5.5 months after identification for controls [42]. Approximately 98% of participants (1,479 cases and 1,520 controls) also completed the validated [45–47] self-administered 101-item modified Block food frequency questionnaire (FFQ). After excluding participants with implausible total energy intake (±3 standard deviations from the mean; n=36), 1,463 cases and 1,500 controls remained in our analysis.

We estimated PUFA intake by linking responses from the FFQ (i.e., grams per day for each line item) with nutrient values available in the U.S. Department of Agriculture databases for ω-3 and ω-6 PUFAs [48]. The following PUFAs were estimated: (1) ω-3 fatty acids, including alpha-linolenic acid (ALA), docosapentaenoic acid (DPA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA); and (2) ω-6 fatty acids, including linoleic acid (LA) and arachidonic acid (AA). An estimate of total PUFA intake was calculated by combining all individual fatty acids. Additionally, an estimate of total ω-3 and ω-6 fatty acids was obtained by summing each individual fatty acid within category (e.g., total ω-3=ALA + DPA + DHA + EPA). We also examined fish/seafood intake according to the items recorded in the FFQ: (1) tuna, tuna salad, tuna casserole; (2) shell fish (shrimp, lobster, crab, oysters,

etc.); and (3) other fish (either broiled/baked). Total fish intake was calculated by summing each of the fish/seafood items recorded in the FFQ.

Statistical analyses

All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95%CI) for the association between PUFA intake and breast cancer risk. PUFA and fish/seafood intake were categorized as quartiles, according to the distribution among controls. Quartiles were selected over other methods of categorization (e.g., tertiles, quintiles, linear, splines) because the shape of the dose-response between exposure and breast cancer incidence was best represented using these cut-points. The relation between any of the PUFA and/or fish and breast cancer incidence was not strictly monotonic [49] thus linear trend tests were not conducted.

Interactions between total ω-3 and total ω-6 intake in association with breast cancer incidence were assessed on the additive (common referent) and multiplicative scales. Additive interaction was evaluated using relative excess risk due to interaction (RERI), with 95% CI [50]. Multiplicative interactions were evaluated by comparing nested models using the Likelihood Ratio Test (LRT) [49]. Total ω-3, total ω-6, and ω-3/ω-6 ratio were dichotomized at the median for use in the interaction models.

We also considered effect modification of the association between PUFA intake and breast cancer risk by: menopausal status (post- vs. pre-menopausal status); and dietary supplement use (yes/no). However, little or no heterogeneity was observed with either of these covariates (data not shown). We also considered potential heterogeneity across breast cancer subtypes, defined by hormone receptor status (any hormone receptor positive breast cancer vs. no hormone receptor positive breast cancer), by constructing polytomous regression models; however, no differences were observed across hormone receptor subtype (data not shown).

All models were adjusted for the frequency matching factor five-year age group. Other potential confounders (including total energy intake, non-steroidal anti-inflammatory drugs (NSAID), family history of breast cancer, income, body mass index, alcohol use, fruit and vegetable intake, and physical activity) were identified using directed acyclic graph [49]. The only covariate that changed the estimates by more than 10% was total energy intake for PUFA intake. All fish intake models included age, energy intake and NSAID use given the possibility that chronic NSAID users experience gastrointestinal problems (e.g., stomach ulcers, reflux) which may subsequently influence diet, including fish consumption [51].

Results

As presented in Table 1, the average intake of total ω-3 fatty acids (1.01 grams per day (SD=0.74)) was lower relative to ω-6 intake [7.66 grams per day (SD=5.68)] among the 1,500 control women in this population-based sample of Long Island residents. The highest contributor to total ω-3 intake was ALA with average intake of 0.86 grams per day (SD=0.71), whereas LA was the highest contributor to total ω-6 intake with an average

intake of 7.59 grams per day (SD=5.66). Tuna intake was reported at higher levels [8.80 grams per day (SD=13.98)] in our control population compared to shell fish intake [3.57 grams per day (SD=9.07)]. Fish was a major contributor to high intake of long-chain ω-3 PUFAs, including DPA, DHA, and EPA. In contrast, foods that contributed to high ALA intake were biscuits/muffins and other fried foods, which was similar to what was observed for LA intake. High AA intake appeared to be driven by eggs and meats, including fish, chicken, and ham.

Multivariable-adjusted odds ratios for the associations between all measures of PUFA intake and breast cancer incidence were imprecise (and most were not statistically significant), as presented in Table 2. For example, elevated odds ratios were observed for high intake of total PUFA, total ω-3, ALA, ω-6, and LA intakes, but CIs were wide. No associations were observed for the long-chain ω-3 PUFA (DPA, DHA, EPA), AA, or high intake of the ω-3/ω-6 ratio.

As shown in Table 3, we observed an interaction between ω-3 and ω-6 intake, which was statistically significant on the additive scale [adjusted RERI=0.41 (95%CI=0.06,0.76)]. Risk reductions for breast cancer were modest for women who consumed low levels of both ω-3 and ω-6 [adjusted OR=0.83 (95%CI=0.63,1.09)], compared to women who consumed high ω-3 and low ω-6. For women who consumed high levels of ω-3 and ω-6, the odds ratios were close to the null value [adjusted OR=0.95 (95%CI=0.72,1.26)]. In contrast, higher intakes of ω-6 fatty acids in conjunction with lower intake of ω-3 fatty acids was associated with an approximately 20% increased breast cancer incidence [adjusted OR=1.20 (95% CI=0.85,1.69)]. The increase observed for this group was super-additive (41% greater) compared to the 22% (=5%+17%) expected risk reduction, derived from the individual ORs for those consuming either high levels (≥median; 5% risk reduction), or low levels (<median; 17% risk reduction) of both ω-3 and ω-6 fatty acids. Similar results were observed when we considered interactions between ω-3 and ω-6 on a multiplicative scale, as shown in Table 4.

Higher intake of total fish, tuna, shell fish, or other fish (broiled/baked) was not associated with breast cancer risk in our study, as presented in Table 5.

Discussion

We are the first to report an additive interaction between ω-3 intake and ω-6 intake in relation to breast cancer risk in a population-based sample of U.S women. Specifically, we observed a 20% increase in the odds of breast cancer among consumers of high levels of ω-6 and low levels of ω-3 compared to those who consumed low levels of ω-6 and high levels of ω-3. The odds ratio for women consuming high ω-6 and low ω-3 was increased, whereas the corresponding estimates for intake of high levels or low levels, of either PUFA class, were reduced. This interaction underscores the importance of considering intake of ω-3 and ω-6 simultaneously when examining associations with breast cancer in the U.S.

No previous U.S. studies have reported the potential interaction between ω-3 and ω-6 PUFAs and breast cancer risk, and only two examined the ratio of ω-3 and ω-6 intakes

[23,30]. Consideration of an interaction may be preferable, given that a ratio measure permits only one type of relation between two exposures, whereas an interaction is more flexible. One previous Shanghai study reported an interaction between ω-3 and ω-6 intake on breast cancer risk [18], with a significant two-fold increased risk for high ω-6 in combination with low marine-derived ω-3 intake. The LIBCSP results presented here for the interaction between ω-3 and ω-6 intake are in the same direction as those reported in the Shanghai study, but less pronounced. Importantly, daily fish consumption in the Shanghai population was almost five times greater than the frequency reported among our Long Island population, which could partially explain the weaker association observed in our study.

The modest positive association between ω-6 PUFA (total ω-6, LA, AA) and breast cancer incidence observed here is similar to associations reported in other studies conducted among Western populations [16,18,28,30,35]. However, our findings for the association between long-chain ω-3 (DPA, DHA, EPA) PUFAs are not consistent with the risk reductions reported by previous studies conducted among Asian and some European populations [16–19,32]. Additionally, the increased risk for ALA intake we observed is inconsistent with the laboratory evidence for inhibition of breast cancer growth [52,53]. However, in other epidemiologic studies, the association between ALA intake and breast cancer risk remains unclear, with some studies reporting increased risks [18,20,29,32,54], and others reporting risk reductions [24,36]. The variation in results across studies may be due to different dietary assessment methods used, consumption of different food sources of ALA (e.g., biscuits/muffins and fried foods were major contributors in our population), or with potential recall bias that can occur in case-control studies. Or, perhaps, ALA reduces breast cancer growth only after conversion to long-chain ω-3 PUFAs. The *in vivo* conversion of ALA to long-chain ω-3 PUFAs is inefficient in the presence of high ω-6 [55]. Thus, it is possible that in populations with high ω-6 intake, benefits of ALA intake are less evident.

The slight breast cancer risk reductions in relation to a high ω-3/ω-6 ratio observed in our study were modest compared to estimates reported in other studies in European [56], Mexican [57], and U.S. populations [23,30]. However, this may reflect the relatively low intake of ω-3 and ω-6 in our study population. Very low intake of both ω-3 and ω-6 PUFAs could result in a high ratio value for ω-3/ω-6 intake (when ω-6 intake is less than 1). Doses in excess of 2 g/day may be required for decreasing prostaglandin E2 production [58,59], a primary inflammatory eicosanoid resulting from AA metabolism, which has been implicated in carcinogenesis [7]. Thus, a high ratio of ω-3/ω-6 derived from low intakes of ω-3 and ω-6 PUFAs may not represent a sufficient dose for ω-3 to exert a beneficial response *in vivo*. In the U.S., only one previous population-based study has considered the PUFA ratio in association with breast cancer risk; utilizing data from the Vitamins and Lifestyle Cohort (VITAL) [30], a 16% risk reduction was observed in association with high ω-3/ω-6 intake ratio. This Western Washington-based study included marine-derived ω-3 intake from both dietary sources and supplements, and thus levels of ω-3 intake were higher than the dietary-derived intake estimates observed in our Long Island-based study. Nonetheless, given the modest risk reductions reported for the ω-3/ω-6 ratio in both studies, examining the interaction between ω-3 and ω-6 intake, rather than the ratio, may be a more favorable strategy in populations where PUFA intake is relatively low.

Strengths of our population-based, case-control study include observation of an interaction between ω-3 and ω-6 on breast cancer development, which has not been previously assessed in a U.S. population. We also examined associations with fish intake (a dietary source rich in ω-3 fatty acids) among women who reside in a geographic area that is surrounded by water, and for whom the variability of fish intake would presumably be greater than for others who reside in more land-locked areas of the U.S [14]. However, we did not observe any notable associations with fish intake and breast cancer incidence, even though women living in New York City [60] have been reported to consume fish greater than the national estimates from NHANES [61].

This study also has limitations. The LIBCSP population includes predominantly Caucasian women, which reflects the racial distribution of the residents of the two source counties on Long Island. Consequently, examination of racial differences was not possible. Our results are therefore generalizable to only Caucasian-American women, for whom breast cancer risk remains high [62].Future studies may also be warranted to evaluate the timing of exposure relative to breast cancer development. FFQ responses are assumed to reflect usual adult diet [63], although recent changes due to a disease diagnosis or treatment regimens could influence those responses. The LIBCSP questionnaires were administered within months of diagnosis, and for two-thirds of women this was prior to the onset of chemotherapy [42], which is likely to reduce the impact of dietary changes and perhaps recall of diet on the FFQ. However, a single dietary assessment via FFQ may not necessarily reflect diet during all etiologically relevant time periods for breast cancer development (i.e., adolescence) [64].

Furthermore, estimating PUFA intake via FFQ linkage with the USDA databases could result in measurement error. For example, the PUFA content measured in the foods reported in the USDA database [48] may differ from those actually consumed by LIBCSP participants due to differences in harvesting, storage, processing, and cooking methods [65–67]. Additionally, we were unable to assess associations with consumption of different fish varieties. This is important given the amount of long-chain ω-3 content found in fish differs by species [61]. However, we assessed tuna intake, which is the most frequently consumed fish variety in the U.S. and is also a major source of dietary ω-3s [14]. PUFA intake via supplements (i.e., fish oil consumption) was not measured as part of the case-control interview. Given fish oil contributes to intake of long-chain ω-3 this could underestimate DHA and EPA consumption in our population. However, in a follow-up interview, 89% of the LIBCSP cases reported never using fish oil supplements approximately five years after diagnosis [68]. Fish oil supplement use has only recently (after 2002) received attention due to is potential risk reductions for cardiovascular disease [69]. Furthermore, use of fish oil supplements increased post-2002 in two large U.S. cohorts [70]. Thus, prevalence of fish oil supplement use at the time of the LIBCSP case-control interview (during years 1996-1997) was likely low and the potential underestimation of DHA and EPA intake may be negligible. Biomarkers could provide an objective measure of PUFA intake; however, biomarkers may reflect different time periods of exposure, ranging from a few days to one year (depending on the type of biomarker used) [71]. Therefore, use of PUFA biomarker measurements in a case-control study may not reflect the etiologically relevant time period for breast cancer development. Future studies, if feasible, should consider multiple prospective biomarker

measurements in order to capture dietary PUFA exposure (including changes in diet) during relevant periods of breast cancer etiology.

In conclusion, we observed among a population-based sample of Long Island residents, women who consume high levels of ω-6 and low levels of ω-3 had an increased risk for breast cancer, compared to women who consume low levels of ω-6 and high levels of ω-3. Our results suggest that high intake of ω-3 PUFA, coupled with low intake of ω-6, may be a potential risk reduction strategy for breast cancer among U.S. women. Further confirmation using an objective measurement of PUFA intake via biomarkers may be warranted.

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List of abbreviations

AA	arachidonic acid
ALA	alpha-linolenic acid
Ca	cases
CI(s)	confidence interval(s)
Co	controls
DPA	docosapentaenoic acid
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FFQ	food frequency questionnaire
g	grams
kcal	kilocalories
LA	linoleic acid
LIBCSP	Long Island Breast Cancer Study Project
LRT	likelihood ratio test
N/A	not applicable
NHANES	National Health and Nutrition Examination Survey
N.Y.	New York
NSAID(s)	non-steroidal anti-inflammatory drug(s)
OR(s)	odds ratio(s)
pct	percentile

PUFA(s)	polyunsaturated fatty acid(s)
RERI	relative excess risk due to interaction
SD	standard deviation
U.S.	United States
VITAL	Vitamins and Lifestyle

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Table 1

Characteristics of polyunsaturated fatty acid intake (PUFA) and fish intake among the population-based sample of control women (N=1500) in the LIBCSP, 1996-1997

Nutrient/Food	Mean	SD	Quartile Cutpoints			Major PUFA-rich foods contributing to high nutrient intake in the LIBCSP
			25th Pct	50th Pct	75th Pct	
Nutrient (g/day)						
Total PUFA[a]	8.67	6.31	4.21	7.27	11.25	Butter, Mayonnaise/salad dressings, safflower/corn oil, margarine, peanuts/peanut butter
Total ω-3[b]	1.01	0.74	0.49	0.83	1.30	Biscuits/muffins, butter, mayonnaise/salad dressings, fish, safflower/corn oil
ALA	0.86	0.71	0.35	0.68	1.14	Biscuits/muffins, French fries/fried potatoes, butter, cookies, mayonnaise/salad dressings
DPA	0.01	0.01	0.01	0.01	0.02	Tuna, fish, chicken, shellfish, beef
DHA	0.09	0.09	0.03	0.06	0.12	Tuna, fish, eggs, shellfish, chicken
EPA	0.04	0.05	0.01	0.03	0.06	Fish, tuna, shellfish, chicken
Total ω-6[c]	7.66	5.68	3.68	6.31	10.10	Biscuits/muffins, French fries/fried potatoes, butter, chips/popcorn, mayonnaise/salad dressings
LA	7.59	5.66	3.65	6.23	9.99	Biscuits/muffins, French fries/fried potatoes, butter, chips/popcorn, mayonnaise/salad dressings
AA	0.07	0.06	0.04	0.06	0.09	Eggs, Fish, chicken, ham/lunch meats, shellfish
ω-3/ω-6	0.15	0.14	0.10	0.14	0.17	N/A
Fish (g/day) [d]						
Total fish[e]	19.62	23.83	4.87	13.23	26.86	N/A
Tuna	8.80	13.98	0.00	4.77	12.40	N/A
Shell fish	3.57	9.07	0.00	0.00	4.62	N/A
Other (broiled/baked)	7.25	10.59	0.00	2.80	10.77	N/A

Note:

[a] Total PUFA = ALA + DPA + DHA + EPA + LA + AA

[b] Total ω-3 = ALA + DPA + DHA + EPA

[c] Total ω-6 = LA + AA

[d] Controls with null values for total fish (N=161), tuna (N=393), shell fish (N=765), and other (N=592) were included in calculations.

[e]Total fish = tuna + shell fish + other (broiled/baked)

LIBCSP = Long Island Breast Cancer Study Project

SD = standard deviation

N/A = not applicable

Table 2

Multivariable[a]-adjusted ORs and 95% CI for the association between dietary PUFA intake and the risk of breast cancer in the LIBCSP, 1996-1997

PUFA	Quartile 1			Quartile 2				Quartile 3				Quartile 4			
	Co	Ca	OR	Co	Ca	OR	95% CI	Co	Ca	OR	95% CI	Co	Ca	OR	95% CI
Total PUFA	375	342	1.00	375	392	1.23	1.00, 1.52	375	386	1.27	1.02, 1.59	375	343	1.25	0.95, 1.63
Total ω-3	375	340	1.00	375	403	1.25	1.01, 1.54	375	377	1.23	0.98, 1.54	375	343	1.20	0.92, 1.58
ALA	375	335	1.00	375	390	1.23	0.99, 1.51	375	389	1.29	1.04, 1.61	375	349	1.25	0.96, 1.62
DPA	375	365	1.00	375	354	0.99	0.81, 1.22	375	375	1.08	0.88, 1.33	375	369	1.09	0.88, 1.36
DHA	375	372	1.00	375	336	0.91	0.74, 1.13	375	369	1.02	0.83, 1.26	375	386	1.06	0.86, 1.31
EPA	375	350	1.00	375	359	1.02	0.83, 1.25	375	365	1.08	0.88, 1.33	375	389	1.14	0.92, 1.40
Total ω-6	375	347	1.00	375	374	1.15	0.93, 1.42	375	405	1.31	1.05, 1.63	375	337	1.18	0.91, 1.55
LA	375	351	1.00	375	367	1.12	0.91, 1.38	375	407	1.30	1.05, 1.62	375	338	1.18	0.90, 1.54
AA	375	371	1.00	375	378	1.05	0.85, 1.29	375	367	1.03	0.83, 1.27	375	347	1.03	0.81, 1.29
ω-3/ω-6	375	360	1.00	375	384	1.09	0.89, 1.34	375	346	0.95	0.77, 1.17	375	373	0.99	0.80, 1.21

Note:

Co=Controls, Ca=Cases, LIBCSP=Long Island Breast Cancer Study Project

[a]Multivariable-adjusted ORs and 95% CI adjusted for matching factor (5-year age group) and total energy intake (kcal/day)

Table 3

Multivariable[a]-adjusted ORs and 95% CI for the additive interaction between dietary ω-3 and ω-6 (high and low intake) and the risk of breast cancer in the LIBCSP, 1996-1997

Model	Low ω-6 (< median)			High ω-6 (≥ median)			RERI[b]	95% CI[c]
	N	OR	95% CI	N	OR	95% CI		
High ω-3 (≥ median)	256	1.00		1,214	0.95	0.72, 1.26		
Low ω-3 (< median)	1,215	0.83	0.63, 1.09	278	1.20	0.85, 1.69	0.41	0.06, 0.76

Note:

Co=Controls, Ca=Cases, LIBCSP=Long Island Breast Cancer Study Project

[a]Multivariable ORs and 95% CI adjusted for matching factor (5-year age group) and total energy intake (kcal/day)

[b]RERI (Relative Excess Risk due to Interaction) = OR_{11} - OR_{10} - OR_{01} +1

[c]95% CI for RERI estimated using Hosmer & Lemeshow [50]

Table 4

Multivariable[a]-adjusted ORs and 95% CI for the multiplicative interaction between dietary ω-3 and ω-6 (high and low intake) and the risk of breast cancer in the LIBCSP, 1996-1997

Model	Low ω-6 (< median)			High ω-6 (≥ median)			LRT χ^{2b}	p value
	N	OR	95% CI	N	OR	95% CI		
High ω-3 (≥ median)	256	1.00		1,214	1.00			
Low ω-3 (< median)	1,215	0.83	0.63, 1.09	278	1.26	0.96, 1.65	4.61	0.03

Note:

Co=Controls, Ca=Cases, LIBCSP=Long Island Breast Cancer Study Project, LRT=likelihood ratio test

[a] Multivariable ORs and 95% CI adjusted for matching factor (5-year age group) and total energy intake (kcal/day)

[b] LRT $\chi 2$ calculated using nested models for the multiplicative interaction.

Table 5

Multivariable[a]-adjusted ORs and 95% CI for the association between fish intake and the risk of breast cancer in the LIBCSP, 1996-1997

	Never			Quartile 1				Quartile 2				Quartile 3				Quartile 4			
Fish	**Co**	**Ca**	**OR**	**Co**	**Ca**	**OR**	**95% CI**	**Co**	**Ca**	**OR**	**95% CI**	**Co**	**Ca**	**OR**	**95% CI**	**Co**	**Ca**	**OR**	**95% CI**
Total fish intake	161	136	1.00	332	348	1.25	0.94, 1.67	335	323	1.13	0.84, 1.50	336	324	1.12	0.84, 1.50	336	332	1.19	0.89, 1.59
Tuna	393	343	1.00	256	241	1.08	0.85, 1.37	285	320	1.24	0.99, 1.55	141	141	1.12	0.84, 1.49	425	418	1.15	0.93, 1.42
Shell fish	765	750	1.00	126	102	0.78	0.58, 1.05	227	245	1.10	0.89, 1.38	178	169	0.99	0.78, 1.26	204	197	1.09	0.86, 1.38
Other fish (broiled/baked)	592	505	1.00	224	253	1.26	1.00, 1.58	87	104	1.38	1.00, 1.91	346	341	1.08	0.88, 1.32	251	260	1.18	0.94, 1.47

Note:

Co=Controls, Ca=Cases, LIBCSP = Long Island Breast Cancer Study Project

[a]Multivariable-adjusted ORs and 95% CI adjusted for matching factor (5-year age group), total energy intake (kcal/day), and NSAID use.