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Interaction between Polyunsaturated Fatty Acids and Genetic Variants in Relation to Breast Cancer Incidence

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Abstract

Higher intake of ω-3 relative to ω-6 polyunsaturated fatty acids (PUFAs) may reduce breast carcinogenesis via different metabolic pathways. The PUFA-breast cancer association remains inconclusive, thus, we hypothesized that interactions between the ratio of dietary ω-3:ω-6 intake and polymorphisms from PUFA-related metabolic pathways would help elucidate an association. Utilizing resources from the Long Island Breast Cancer Study Project, a population-based case-control study (n=1035 cases/1075 controls), we examined interactions between ω-3:ω-6 ratio and 18 polymorphisms of 15 genes. Compared to the putative lowest risk group (high ω-3:ω-6, low-risk *FASL* rs763110 CT/TT genotype), the odds ratio (OR) for breast cancer from unconditional logistic regression models was weakly increased for other exposure-genotype combinations (high ω-3:ω-6, high-risk *FASL* CC genotype, OR=1.18, 95% confidence interval (CI)=0.90, 1.53; low ω-3:ω-6, CT/TT genotype, OR=1.35, 95% CI=1.09, 1.66); but was approximately null for the putative highest risk group (low ω-3:ω-6, CC genotype; OR=1.06, 95% CI=0.81, 1.38). We observed an interaction between the ω-3:ω-6 ratio and *FASL* rs763110 on the additive scale [Relative Excess Risk Due to Interaction (RERI)=-0.47, 95% CI=-0.92, -0.02]. Interactions with other polymorphisms considered were not evident. Our findings suggest that the PUFA-breast cancer association may be modified by *FASL*. However, additional research is needed given this interaction may be due to chance and is inconsistent with our *a priori* biologic hypothesis.

Keywords: Breast cancer; Epidemiology; Fat/omega-3; Omega-6/fish oil; Single nucleotide polymorphisms

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Introduction

Experimental evidence suggests that higher ω-3 relative to ω-6 could reduce mammary carcinogenesis through mechanisms related to inflammation, oxidative stress, and estrogen metabolism [1]. A recently published meta-analysis of population-based prospective cohort studies reported an approximately null association for dietary intake of polyunsaturated fatty acids (PUFAs) among studies that were conducted using populations from the United States (U.S.) [2]. This is inconsistent with findings from studies conducted in Asia [3] that show risk reductions for ω-3 intake. PUFAs may affect carcinogenesis via multiple biologic pathways [1]. Thus, we hypothesized that interactions with biologically relevant genetic polymorphisms with breast cancer may help to clarify the biologically plausible association with

PUFAs. We further hypothesized that consideration of the ratio of ω-3 to ω-6 intake (ω-3:ω-6) may enhance our examination of interactions with breast cancer, given the two PUFA subgroups compete for the same metabolic enzymes [1]. Potential effect measure modification by genetic polymorphisms involved in PUFA metabolism has been previously considered by two studies [4,5] which examined only ω-3, but not intake relative to ω-6. Further, each study considered either glutathione *S*-transferase (GST) [4] or lipoxygenase enzymes [5], but not other genes involved in other biologically plausible pathways.

Materials and Methods

To address our hypothesis that the interaction between PUFA intake and breast cancer incidence would be evident when we considered the interaction between the ratio of ω-3:ω-6 intake and multiple genetic polymorphisms in the inflammation, oxidative stress, and estrogen metabolism pathways, we used case-control resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study. Details of the parent study methods have been published [6].

Study population

Cases were women diagnosed with first primary *in situ* or invasive breast cancer between August 1, 1996 and July 31, 1997, who were residents of Nassau and Suffolk counties on Long Island, NY. Cases were identified by contacting hospital pathology departments daily or 2-3 times per week. Controls were identified from these same two counties using random digit dialing (women <65 years), and Health Care Finance Administration rosters (women ≥ 65 years). Controls were frequency-matched to the expected age distribution of the cases by 5-year age group. The LIBCSP includes 1508 case and 1556 control participants, ranging in age from 20 to 98 years. Approximately 67% were postmenopausal, and 93% self-reported as white, which is consistent with the underlying distribution of Nassau and Suffolk counties at the time of data collection.

Dietary and covariate assessment

LIBCSP participants completed an interviewer-administered risk factor questionnaire within approximately three months of diagnosis (cases), and within six months of identification (controls). Nearly all cases (98%) and controls (98%) completed a self-administered 101-item modified Block food frequency questionnaire (FFQ) to assess dietary intake in the year prior to the interview. PUFA intake was estimated by linking FFQ responses with nutrient values available from the U.S. Department of Agriculture databases for total ω-3 and total ω-6 PUFAs [7]. Alpha-linolenic acid, docosapentaenoic acid, eicosapentaenoic acid, and docosahexanoic acid were included in the estimate for total ω-3 intake; whereas, linoleic acid and arachidonic acid subtypes comprised the estimate for total ω-6 intake. Excluding individuals with extreme total energy intake (>3 standard deviations from the mean) yielded 1463 cases and 1500 controls. Given ω-3 and ω-6 compete for the same enzymes [1], we primarily considered the ratio of ω-3:ω-6 intake [which ranged from 0.10-0.17 (25-75th percentiles, respectively) among controls [3]. However, because this ratio may not accurately represent absolute intakes for each PUFA individually, we also considered separately total ω-3 and ω-6 (with corresponding ranges from 0.49-1.30 and 3.68-10.10 grams/day, respectively [3]).

Genotyping

Blood samples were collected from cases (74%) and controls (74%) at the time of the case-control interview and were used as the DNA source for genotyping [8-14]. Briefly, DNA was isolated from mononuclear cells in whole blood, which was separated by Ficoll (Sigma Chemical Co., St. Louis, MO) using standard phenol and chloroform-isoamyl alcohol extraction and RNase treatment [10]. Genotyping for inflammation genes [*PTGS-2* (rs201417, rs5275), *FAS* (rs2234767, rs1800682), *FASL* rs763110, *PPAR-α* rs1800206, *TNF-α* rs1800629] used the following assays: Taqman 5'-Nuclease Assay (Applied Biosystems, Foster City, CA) and AcycloPrime^{TM}-FP SNP Detection Kit obtained from Perkin Elmer Life Sciences (Boston, MA) [9,11,12]. The same assay was used for aromatase gene [*CYP17* rs743572 with a 10 μM probe [8,14]]. For oxidative stress genes (*CAT* rs1001179, *MPO* rs2333227, *MnSOD* rs4880, *GPX1* rs1050450, *GSTA1* rs3957356, *GSTP1* rs1695, *COMT* (rs4680, rs737865)], BioServe Biotechnologies (Laurel, MD) performed the genotyping using high-throughput, matrix assisted, laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry of Sequenom, Inc. (San Diego, CA). Gene deletions for *GSTM1* and *GSTT1* were determined by a multiplex polymerase chain reaction method, with the constitutively present gene β-globulin as an internal positive control [13].

Eighteen polymorphisms in 15 genes were selected spanning three biologically plausible pathways for PUFA metabolism, including inflammation, oxidative stress, and estrogen metabolism pathways. Variants affecting polyphen prediction (*GPX1*), transcription factor binding prediction (*PTGS-2* rs20417, *FAS*, *FASL*, *TNF-α*, *MPO*, *CAT*, *GSTA1*, *COMT* rs737865, *CYP17*), miRNA binding (*PTGS-2* rs5275, *GPX1*), 3D conformation (*PPAR-α*, *COMT* rs4680), or splicing regulation (*PPAR-α*, *FAS* rs2234767, *GPX1*, *GSTP1*, *COMT* rs4680) were considered as putatively functional variants as defined in the NIEHS SNPInfo WebServer [15].

Data were missing for some genetic polymorphisms, primarily due to laboratory failures. The final analytic sample size included a maximum of 1035 cases and 1075 controls, but varied by genetic variant (**Supplemental Table S1**).

Tests for Hardy-Weinberg equilibrium (HWE) were conducted among controls. Only *PTGS-2* rs20417 and *MPO* deviated significantly from HWE (p=0.003 and 0.04, respectively). However, the observer agreement for *PTGS-2* and *MPO* in 8% of a randomly selected sample was high (κ=0.99 and 0.91, respectively), and the failure rate was low for both polymorphisms (<1%). Also, the allele frequencies for both polymorphisms were similar to other studies [16].

Statistical analysis

Unconditional logistic regression was used to estimate interactions on the additive (using single-referent) and multiplicative (using a multiplicative interaction term) scales. To maximize cell sample size, PUFA intake measures were dichotomized at the median

value (ratio of ω-3:ω-6=0.14, ω-3=0.83, and ω-6=6.31), and genotypes were dichotomized according to a dominant model and categorized into "high" and "low" risk groups based upon the putative function of the variant allele, which was determined using the existing literature (**Supplemental Table S1**). Additive interactions were evaluated using the Relative Excess Risk Due to Interaction (RERI) and the corresponding 95% CI [17]. Multiplicative interactions were evaluated using the likelihood ratio test (LRT, α=0.05). From among known risk factors for breast cancer, we identified no potential confounders, using a change-in-estimate criterion of 10%. Thus, all interaction models were adjusted for the frequency matching factor five-year age group and total energy intake (kcal/day). We considered multiple comparisons using the false discovery rate (FDR, *q*=0.05) [18]. Analyses were conducted using SAS, version 9.2 (Cary, NC).

Results

When we explored interactions between the ratio of ω-3:ω-6 intake and genetic polymorphisms in the inflammatory, oxidative stress, and estrogen metabolism pathways, we found little evidence to support an additive **(Table 1)** or multiplicative (**Supplemental Table S2**) interaction for the majority of polymorphisms considered. However, an interaction was observed on the additive (RERI=-0.47, 95% CI=-0.92, -0.02) and multiplicative scales (LRT χ^2=4.63, *p* value=0.03) for *FASL* rs763110. Specifically, we observed reduced OR for breast cancer among those with a low ratio of ω-3:ω-6 intake with the high risk *FASL* genotype on the multiplicative scale (OR=0.79, 95% CI=0.61, 1.02). The estimate was null on the additive scale (OR=1.06, 95% CI=0.81, 1.38), which was nearly 50% less than what would have been observed under an additive model [(expected ORs=1.52 (additive), and 1.58 (multiplicative)] as indicated by the statistically significant RERI. For the majority of other interactions examined, breast cancer risk remained high for low ratio of ω-3:ω-6 intake regardless of genotype, with the exception of the *FASL* rs763110 and *COMT* rs4680. When we considered PUFA types separately, no additive interaction was observed between total ω-3 intake and *FASL* (RERI=0.02; 95% CI=-0.33, 0.68); but for total ω-6 intake the interaction (RERI=-0.17, 95% CI=-0.59, 0.24) was in a similar direction to what was observed for the ω-3:ω-6 ratio. However, after considering multiple comparisons, we could not rule out chance as an explanation for our findings.

Discussion

In our study we examined the interaction between PUFA intake and genetic polymorphisms from three biologically plausible pathways with breast cancer, and observed multiplicative and additive interaction between *FASL* rs763110 and the ratio of ω-3:ω-6 intake among a population-based sample of women from Long Island, NY. However, we could not rule out chance after adjusting for multiple comparisons. No other notable interactions were observed for polymorphisms from the inflammatory, oxidative stress, and estrogen metabolism pathways with breast cancer incidence.

For the interaction observed with *FASL* rs763110 high-risk genotype, we found a reduced OR for those women with a low ratio of ω-3:ω-6 PUFAs, which was contrary to our *a priori* biologic hypothesis. Amplification of *FASL* has been reported among breast cancer cases [19], and the arachidonic acid-derived eicosanoid, prostaglandin E2 (PGE2), has been reported to increase FASL production [20]. Thus, *a priori* we hypothesized that the allele suggested to increase basal expression of FASL (*i.e.*, C allele) along with low ratio of ω-3:ω-6 intake would increase breast cancer risk. A meta-analysis examining *FASL* rs763110 also reported increased risk for breast cancer for the same high risk allele [21] (although the authors did not consider interactions with PUFA intake). It is possible that the effect of FASL expression may be more important when considered as part of the FAS-FASL ligand-receptor system (part of the tumor necrosis factor superfamily) which can lead to apoptosis [22]. Thus, apoptosis resulting from FAS-FASL ligand-receptor system could potentially explain the reduced risk observed for the hypothesized highest risk subgroup in our study. Previously reported main effects for *FASL* and breast cancer incidence were nearly null in the LIBCSP [9]. Given these LIBCSP findings, the interaction between PUFAs and *FASL* requires further investigation.

Our study expands upon the limited findings from two previous breast cancer studies [4,5], which considered only ω-3 interactions with GSTs or lipoxygenases. Our approach has several advantages, including consideration of interactions between the ω-3:ω-6 ratio and genes involved in multiple biologically plausible pathways related to PUFA metabolism, which we evaluated on additive and multiplicative scales. We also utilized a population for whom dietary intake of total ω-3 PUFAs is likely to be higher compared to the other regions in the U.S.; women in New York City have been reported to consume more fish, a major dietary source of ω-3 PUFAs, compared to estimates from the National Health and Nutrition Examination Survey (NHANES) [23]. We did not observe an association between ω-3:ω-6 ratio and breast cancer incidence in a previous report [3]. However, it is still statistically and biologically possible that examining PUFA-gene interactions in multiple relevant biologic pathways, among a population with relatively high fish intake (a major ω-3 source) [3], could have revealed noteworthy effect modification.

There are several limitations to our study. First, our results are generalizable to only European-American women, for whom the incidence of breast cancer compared to other racial/ethnic groups remains high [24]. Importantly, it is possible that the frequency of the at-risk allele for relevant PUFA metabolism genes differ by racial subgroup [25], and thus it may be important to identify whether the PUFA-gene interactions and breast cancer risk vary among different populations. Furthermore, although we examined interactions with multiple polymorphisms spanning several biologic pathways, our selected genes are not exhaustive. For studies with larger sample sizes, it may be beneficial to examine additional genetic polymorphisms, such as genes involved in the *in vivo* metabolism of ω-3 and ω-6. Finally, after adjusting for multiple comparisons, we could not rule out chance for the interaction with *FASL* rs763110. However, we selected variants based on their putative function, thus, correcting for multiple comparisons may be overly conservative.

In this first study to consider the interaction between ω-3:ω-6

Table 1 Multivariable[a]-adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for the risk of breast cancer for the interaction between ω-3/ω-6 ratio and putatively functional genetic polymorphisms[b] evaluated on the additive scale in the LIBCSP, 1996-1997.

Variant	Genotype	High ω-3/ω-6 (≥ median[c])			Low ω-3/ω-6 (<median)			RERI[d]	95% CI[e]
		Ca/Co	OR	95% CI	Ca/Co	OR	95% CI		
PTGS-2	GC/CC	169/198	1.00		208/204	1.26	0.95, 1.67		
rs20417	GG	311/333	1.09	0.84, 1.41	342/341	1.23	0.95, 1.59	-0.12	-0.54, 0.30
PTGS-2	TC/CC	264/310	1.00		306/309	1.23	0.98, 1.55		
rs5275	TT	217/222	1.15	0.89, 1.47	246/232	1.30	1.02, 1.66	-0.08	-0.49, 0.33
PPAR-α	GC/GG	51/48	1.00		50/44	1.12	0.63, 1.98		
rs1800206	CC	354/416	0.77	0.51, 1.18	423/429	0.96	0.63, 1.46	0.06	-0.55, 0.68
FAS	GA/AA	115/145	1.00		123/106	1.57	1.09, 2.24		
rs2234767	GG	364/387	1.19	0.89, 1.58	428/438	1.29	0.97, 1.71	-0.46	-1.06, 0.14
FAS	GG	114/144	1.00		160/157	1.39	0.99, 1.94		
rs1800682	GA/AA	360/386	1.22	0.91, 1.62	390/384	1.39	1.04, 1.84	-0.22	-0.73, 0.28
FASL	CT/TT	312/363	1.00		396/361	1.35	1.09, 1.66		
rs763110	CC	170/169	1.18	0.90, 1.53	157/182	1.06	0.81, 1.38	-0.47	-0.92, -0.02
TNF-α	GG	346/381	1.00		412/403	1.18	0.96, 1.44		
rs1800629	GA/AA	127/145	0.96	0.73, 1.27	134/140	1.12	0.85, 1.48	-0.02	-0.43, 0.40
MnSOD	CC	113/118	1.00		137/141	1.07	0.75, 1.51		
rs4880	CT/TT	353/402	0.92	0.68, 1.23	403/396	1.12	0.83, 1.50	0.14	-0.26, 0.53
MPO	GG	289/304	1.00		340/329	1.14	0.91, 1.43		
rs2333227	GA/AA	183/221	0.87	0.68, 1.13	203/209	1.08	0.83, 1.39	0.06	-0.30, 0.41
CAT	CT/TT	185/180	1.00		210/200	1.06	0.80, 1.41		
rs1001179	CC	283/341	0.80	0.62, 1.04	331/338	1.00	0.77, 1.29	0.14	-0.20, 0.47
GPX1	CT/TT	263/297	1.00		287/255	1.34	1.05, 1.70		
rs1050450	CC	208/226	1.05	0.82, 1.35	255/283	1.08	0.85, 1.37	-0.31	-0.73, 0.10
GSTM1	null	221/208	1.00		236/235	0.99	0.76, 1.29		
deletion	present	218/266	0.77	0.59, 1.00	271/261	1.02	0.79, 1.32	0.26	-0.06, 0.58
GSTP1	AG/GG	236/263	1.00		263/269	1.14	0.89, 1.46		
rs1695	AA	229/248	1.03	0.80, 1.33	271/261	1.23	0.96, 1.57	0.05	-0.33, 0.43
GSTT1	null	99/102	1.00		104/112	1.02	0.69, 1.50		
deletion	present	345/379	0.94	0.68, 1.28	409/396	1.11	0.82, 1.52	0.16	-0.26, 0.57
GSTA1	GA/AA	329/343	1.00		350/347	1.10	0.89, 1.37		
rs3957356	GG	143/181	0.83	0.63, 1.08	191/191	1.10	0.86, 1.42	0.17	-0.18, 0.53
COMT	AG/AA	347/414	1.00		393/383	1.28	1.05, 1.57		
rs4680	GG	130/112	1.37	1.02, 1.83	150/155	1.20	0.92, 1.56	-0.45	-0.97, 0.07
COMT	CC	38/50	1.00		61/60	1.34	0.77, 2.34		
rs737865	CT/TT	427/474	1.16	0.74, 1.81	476/478	1.35	0.87, 2.11	-0.15	-0.87, 0.58
CYP17	TT	168/204	1.00		177/171	1.34	1.00, 1.81		
rs743572	TC/CC	295/310	1.16	0.89, 1.50	361/358	1.28	1.00, 1.65	-0.22	-0.68, 0.24

[a]All models adjusted for matching factor, 5-year age group, and total energy intake (kcal/day).

[b]Genotypes dichotomized using dominant genetic model. The hypothesized lowest risk group (referent group) represents the low risk genotype for PUFA-gene interaction and high ω-3/ω-6 intake. The hypothesized highest risk group represents high risk genotype for PUFA-gene interaction and low ω-3/ω-6 intake. Determination of high risk genotypes was based upon previous literature for the function of the variant allele **(Supplementary Table S1)**.

[c]Median ω-3/ω-6 ratio in the LIBCSP=0.14.

[d]RERI (Relative Excess Risk Due to Interaction)=OR_{11}-OR_{10}-OR_{01}+OR_{00} (e.g., RERI for *PTGS-2* rs20417=1.23-1.26-1.09+1.00=-0.12)

[e]95% CI for RERI estimated using Hosmer and Lemeshow [17]

Note: LIBCSP=Long Island Breast Cancer Study Project; Ca=cases; Co=controls, RERI=Relative Excess Risk Due to Interaction

ratio and genetic polymorphisms from three biologically plausible pathways with breast cancer incidence, we noted an interaction on additive and multiplicative scales for *FASL* rs763110, but not for the other 17 polymorphisms considered. Additional research is needed to help clarify our findings, which were not consistent with our *a priori* hypothesis nor could we rule out chance once we adjusted for multiple comparisons.

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