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A breast cancer case-control study of polybrominated diphenyl ether (PBDE) serum levels among California women

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ABSTRACT

Purpose: Polybrominated diphenyl ethers (PBDEs) are among the most persistent and pervasive global environmental contaminants. Their toxic and endocrine-disrupting properties have made them a focus of concern for breast cancer. Our objective was to evaluate the risk of breast cancer associated with serum PBDE levels in a case-control study nested within the California Teachers Study.

Methods: Participants were 902 women with invasive breast cancer (cases) and 936 with no such diagnosis (controls) who provided 10 mL of blood and were interviewed between 2011 and 2015. Blood samples were collected from cases an average of 35 months after diagnosis. PBDEs were measured in serum using automated solid phase extraction and gas chromatography/high resolution mass spectrometry. Statistical analyses were restricted to the three congeners with detection frequencies ≥75%: 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47), 2,2′,4,4′,6-pentabromodiphenyl ether (BDE-100), and 2,2′,4,4′,5,5′-hexabromodiphenyl ether (BDE-153). Unconditional logistic regression was used to estimate multivariable-adjusted odds ratios (ORs) and their 95% confidence intervals (CI) for each BDE congener, adjusting for serum lipids and other potential confounders.

Results: The OR for each of the three BDE congeners was close to unity with a CI that included one. Analyses stratified by menopausal status, tumor hormone responsiveness, BMI, and changes in body weight yielded similarly null results.

Conclusions: Our findings provide no evidence that serum levels of BDE-47, BDE-100 or BDE-153 are associated with breast cancer risk. These results should be interpreted in the context of study limitations which include the reliance on PBDE measurements that may not represent pre-diagnostic, early-life or chronic exposures and a lack of information on genetic polymorphisms and other factors which may affect endogenous estrogen levels.

1. Introduction

Breast cancer is the leading cancer among women in the United States, with an estimated 266,120 new cases expected to be diagnosed in 2018 (National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER), 2013). Established risk factors account for only a fraction of the cases that occur (Cogliano et al., 2011; Madigan et al., 1995). Increasing rates of breast cancer during the latter half of the last century, coupled with the observation of elevated rates in industrialized and urban areas, has led to speculation that environmental pollutants may play a role in breast cancer etiology (Brody et al., 2007; Gray et al., 2017; Salehi et al., 2008). Polybrominated diphenyl ethers (PBDEs) are a family of synthetic brominated chemicals consisting of over 200 congeners. Introduced in the 1970s, PBDEs were added as flame retardants to a variety of consumer products including polyurethane foam cushioning in furniture and carpet padding, hard plastic casings in appliances and electronics, and in upholstery and other household textiles (Agency for Toxic Substances and Disease Registry (ATSDR), 2015; U.S. Environmental Protection Agency (EPA), 2017). After decades of widespread use, PBDEs have migrated from these products into

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the environment. Owing to their highly persistent and bioaccumulative nature, they have become major persistent organic pollutants (POPs), detected in nearly all environmental media tested, as well as in wildlife and human tissue (Betts, 2008; Costa et al., 2008; Darnerud et al., 2001; Environmental Working Group, 2007; Hites, 2004; Lorber, 2008; United States Environmental Protection Agency, 2008; Sjodin et al., 2008).

Interest in the PBDEs as potential human carcinogens stems from their similar structure and toxicological properties to polychlorinated biphenyls (PCBs), which are known human chemical carcinogens (Betts, 2008; Lorber, 2008; McDonald, 2002; Siddiqi et al., 2003; Lauby-Secretan et al., 2013). Moreover, interest in breast cancer, which is a hormonally-mediated disease, has been driven by a substantial body of laboratory evidence demonstrating endocrine-disrupting effects of PBDEs, including the ability to alter in vivo circulating sex hormone concentrations, enhance estrogenic-like cellular proliferation in MCF-7 cell lines, and interact with estrogen and androgen signaling pathways (Costa et al., 2008; Darnerud, 2008; Gregoraszczuk et al., 2008; Hamers et al., 2006; He et al., 2008; Meerts et al., 2001; Mercado-Feliciano and Bigsby, 2008a, 2008b; Talsness, 2008; Talsness et al., 2008; Legler, 2008; Lyche et al., 2015; Karpeta and Gregoraszczuk, 2017; Karpeta et al., 2016; Kwiecinska et al., 2011). None of the PBDEs have been formally evaluated for carcinogenicity by the International Agency for Research on Cancer. Only one PBDE congener (BDE-209) has been evaluated by the United States Environmental Protection Agency (US EPA), which classified it as a 'suggestive' human carcinogen in 2008 (U.S. Environmental Protection Agency, 2008). More recently, however, the US National Toxicology Program conducted a rodent bioassay for a mixture of BDEs consisting of BDE-47, BDE-99 and BDE-153 (predominant congeners in what was once the most-commonly used commercial BDE formulation) and concluded there was 'clear evidence of carcinogenicity', primarily based on associations found with several hepatic cancers in rodent models (U.S. Environmental Protection Agency (EPA), 2017; US Department of Health and Human Services, 2015).

Human data are sparse. Only a handful of small case-control studies have evaluated PBDEs and cancer risk. Increased risks have been reported for testicular cancer (Hardell et al., 2006) and childhood acute lymphoblastic leukemia (Ward et al., 2014). The epidemiologic evidence for thyroid cancer is mixed, with one studying reporting no association (Aschebrook-Kilfoy et al., 2015) while another reporting elevated risks associated with BDE-209 measured in household dust (Hoffman et al., 2017). Neither of the two small breast cancer studies conducted to date found a significant association with PBDEs (Holmes et al., 2014; Hurley et al., 2011).

The objective of the current study was to evaluate the risk of invasive breast cancer associated with serum PBDE levels among 1838 women participating in a case-control study nested within the California Teachers Study (CTS) cohort.

2. Materials and methods

2.1. Study population

The study participants were drawn from the CTS, an on-going prospective cohort study of 133,479 female California public school professionals initiated in 1995–1996 primarily to study breast cancer. Details of the creation and conduct of the CTS are published elsewhere (Bernstein et al., 2002). Briefly, since the CTS was established via responses to a mailed questionnaire, the cohort has been followed annually for cancer diagnoses, deaths, and changes of address. State and national mortality files, as well as reports from relatives, are used to ascertain dates and causes of death. Address changes for continued follow-up are obtained by several methods including annual mailings, notifications of moves received from participants, and linkages to nationwide consumer reporting companies and the U.S. Postal Service National Change of Address database. Cancer outcomes are identified through annual linkages with the California Cancer Registry (CCR), a legally mandated statewide population-based cancer reporting system. Case ascertainment for the CCR is estimated to be 99% complete and 99% of breast cancer tumors are pathologically confirmed (California Cancer Registry (CCR) California Department of Health, 2017).

2.2. Case and control selection

Cases and controls included in the present analysis were drawn from CTS members who had provided a blood sample and completed an interview-administered questionnaire as part of their participation in a separately-funded breast cancer case-control study nested within the CTS cohort. Case selection criteria for the nested case-control study included: diagnosis with invasive breast cancer (SEER Site code = 26,000) between January 1, 2006 and August 1, 2014 prior to age 80 years; having no prior history of invasive or in situ breast cancer when joining the cohort; and having lived continuously in California from cohort entry until date of diagnosis with invasive breast cancer. Controls were drawn from a probability sample of at-risk CTS cohort members who had no diagnoses of invasive or in situ breast cancer and were frequency matched to breast cancer cases by age at cohort entry (5-year age groups), race/ethnicity and broad geographic region (corresponding to the three field study collection sites). Participation rates were approximately 55% for controls and 65% for cases. Actively refusing to participate was the most common reason for non-participation (29% of controls, 21% of cases), followed by inability to contact (12% for controls, 9% for cases). Approximately 4% of controls and 5% of cases were excluded due to illness or death. Participants in the current analyses were 902 invasive breast cancer cases and 936 controls who participated in the larger CTS nested case-control study and who provided a blood specimen between November 2011 and August 2015 and completed an interview-administered questionnaire at blood draw. Blood specimens from cases were collected an average of 35 months after invasive breast cancer diagnosis (range of interval between diagnosis date and date of specimen collection was 9 months to 8.5 years). Informed consent was obtained from all individual participants included in the study.

2.3. Serum collection

Non-fasting blood samples were collected, most frequently in participants' homes, by licensed phlebotomists into a 10 mL BD® tube (catalog#367985, Becton Dickinson, Franklin Lakes, NJ) with clot activator, double gel for transport, and silicone coated interior, using standard phlebotomy techniques. Prior to field processing, specimens were kept on cool packs for at least 30 min. Within hours of collection, phlebotomists separated the serum portion using portable centrifuges to spin down the clotted blood samples. Processed samples were then frozen and stored at −20 °C for 4–6 weeks until transported either via local courier (on cool-packs) or overnight (on dry-ice via FedEx) to the laboratory for chemical analysis. Samples remained frozen during this transportation process. Upon receipt at the laboratory, specimens were stored at −20 °C until analysis.

2.4. PBDE measurements

Serum samples were analyzed for 19 BDE congeners by the Environmental Chemistry Laboratory at the California Department of Toxic Substances Control (Berkeley, CA). Samples were thawed and aliquoted for PBDE and lipid measurements. Automated solid phase extraction (SPE; Biotage, Uppsala, Sweden) and gas chromatography/high resolution mass spectrometry (GC-HRMS, DFS, ThermoFisher, Bremen, Germany) were used for the analysis of PBDEs (Park et al., 2015). Briefly, thawed serum samples (2 mL) were fortified with a panel of $^{13}C_{12}$ labeled surrogate standards and mixed well. Equal volumes

(4 mL) of formic acid and water were added into each sample before loading on the SPE modules. Oasis HLB cartridges (3 cc, 500 mg, Waters Co., Milford, MA, USA) and acidified silica (500 °C pre-baked, manually packed, 3 cc) were used for the sample extraction and clean-up, respectively. The collected final eluates in hexane: dichlomethane (1:1) were concentrated in TurboVap (Biotage, Charlotte, NC, USA), and spiked with recovery standards. Standard reference material (SRM 1958, National Institute of Standards and Technology, Gaithersburg, MD, USA) and bovine serum pre-spiked with known amounts of target analytes were used as QA/QC samples. The laboratory is proficient in the analysis of PBDEs as demonstrated by its regular participation in the performance evaluation system managed by the Arctic Monitoring & Assessment Program (AMAP). PBDE assays yielded concentrations reported in ng/mL wet weight. A small volume of sera from each sample was sent to Boston Children's Hospital for measurement of total cholesterol and triglycerides by enzymatic methods (Allain et al., 1974; Stinshoff et al., 1977). Cholesterol and triglycerides were used to calculate total lipid content based on Phillips' formula (Phillips et al., 1989). Detection frequencies varied widely by congener, ranging from < 1% for BDE-17 to approximately 87% for BDE-47 (Supplemental Table S1).

2.5. Covariate information

Information on potential covariates was derived from a series of mailed surveys (a baseline questionnaire completed in 1995–1996 at CTS enrollment and five follow-up surveys), as well as a survey administered by an interviewer at the time of blood draw. Factors considered as potential covariates included established breast cancer risk factors (based on a review of the literature) as well as factors that prior exploratory analyses had identified as correlates to serum PBDE levels in this study population. This initial set of potential covariates included information on: demographics (age, race, neighborhood socioeconomic status and urbanization); timing of blood draw (date and season of blood collection); behavioral factors (smoking, alcohol consumption, physical activity, use of menopausal hormone therapy (HT)); diet (total fat, fiber, vitamin D, calories, red meat, pork, fish, and total meat consumption); body mass index (BMI = weight in kg divided by square of height in meters) and changes in body weight; family history of breast cancer; and reproductive history (age at menarche, age at first full term pregnancy, lactation history, menopausal status).

2.6. Statistical analysis

All analyses were conducted in SAS Version 9.04 (SAS Institute Inc. and SAS Institute Inc., 2007). Statistical significance was defined at a p-value < 0.05. Concentrations below the LOD for which no signal was detected were estimated by single imputation from a log-normal probability distribution based on the observed distribution of quantified measurements, following the method suggested by Lubin et al. (2004). In order to minimize potential biases associated with imputing high frequency of non-detectable levels, only the three congeners with detection frequencies (DF) of 75% or more were included in our risk analyses. These included: 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47), 2,2′,4,4′,6-pentabromodiphenyl ether (BDE-100), and 2,2′,4,4′,5,5′-hexabromodiphenyl ether (BDE-153).

Prior to conducting the risk analyses, a number of exploratory and descriptive analyses were conducted. Spearman rank correlation coefficients (r) between BDE congeners were calculated. Because the congeners were highly correlated, we considered each PBDE separately in our risk analyses.

The risk of breast cancer associated with each BDE congener was estimated by unconditional logistic regression using PROC LOGISTIC to generate odds ratios (OR) and 95% confidence intervals (95% CI). These models were run on the measured and imputed wet weight values (expressed as $\log_{10}$ [BDE, ng/mL]), adjusting for total serum lipid content by the addition of a separate term in the model (expressed as $\log_{10}$ [total lipids, ng/mL]), as recommended by Schisterman et al. (2005). Smoothing splines were considered in generalized additive models (using PROC GAM) and evaluated to assess potential non-linearities in the relationship between each PBDE and the log-odds of breast cancer but no evidence of non-linearity was observed. In addition to estimating breast cancer risks for the log-linear continuous values of PBDE concentrations, we also estimated risks for quartiles of PBDE concentrations based on the distribution among controls.

Minimally-adjusted crude ORs were generated from models that included adjustment only for total serum lipids and the matching design variables (age at enrollment, race/ethnicity, and study site). Fully-adjusted multivariable models were built via a two-step process. First, a backwards elimination approach was used, starting with a model that forced inclusion of the BDE variable, the matching design variables, and serum lipid content and retention of covariates for which the p-value for the Wald chi-square was < 0.05. We then further evaluated potential confounders by adding each of the excluded variables back into the model one at a time and evaluated the change in the estimated OR for the BDE variable. Factors that changed the estimated OR for the BDE by ≥10% were retained in our final multivariable models. While we conducted this process separately for each BDE, it resulted in the same set of covariates for all congeners. Final multivariable models included terms for: age at baseline, race/ethnicity, study site, total serum lipid content, date of blood draw, season of blood draw, BMI at baseline, long-term moderate and strenuous physical activity, family history of breast cancer, parity/age at first full term pregnancy, menopausal status/HT use, and pork consumption at baseline (see Table 1 for details of how these factors were specified in the models).

To evaluate whether risks differed within certain subsets of our study population, a number of stratified analyses were conducted. Subsets of interest were chosen a priori based on our review of the literature. Selected subsets included: pre/peri-menopausal versus post-menopausal women; cases with hormonally responsive tumors, identified as estrogen or progesterone receptor positive (ER+/PR+) versus non-hormonally responsive tumors that were estrogen-receptor negative and progesterone-receptor negative (ER-/PR-); women who had and had not ever used menopausal HT; women with low, medium and high BMI; women who had and had not ever breastfed; women who reported changes in body weight versus those with stable body weight (≤5 pound change in body weight between enrollment in the study in 1995–1996 and the 2011–2012 mailed survey). Additionally, to explore whether risks were confined to women who may have been exposed to PBDEs during critical windows of susceptibility, we examined risks among women who entered menopause or experienced their first full-term pregnancy between 1990 and 2000 – the interval of time when U.S. population PBDE exposures were likely at their peak (Guo et al., 2016; Petreas et al., 2003; She et al., 2002; Sjodin et al., 2004). Due to small numbers in some subsets, regression models for these analyses were adjusted only for the matching design variables and total serum lipids.

Two additional analyses were conducted to indirectly evaluate potential biases that could have been introduced by the post-diagnostic assessment of serum PBDE concentrations. These included: 1) evaluating the Spearman Rank correlations between PBDE serum concentrations and the time interval between diagnosis and blood draw; and 2) repeating our logistic regression analyses, stratified by the time interval between diagnosis and blood draw (≤3 years and > 3 years).

3. Results

Participants were predominantly middle-aged and older non-Hispanic white women, reflecting the characteristics of the CTS cohort from which they were selected. The median age of study participants at CTS baseline enrollment was 49 years (range = 24–71) and was 66 years (range = 41 to 87) at the time of blood collection for this

Table 1
Distribution of selected characteristics for 1838 study participants.[a,b]

Characteristic[b]	Case		Control		All	
	N	Percent	N	Percent	N	Percent
All participants	902	100	936	100	1838	100
Age at baseline questionnaire (years)[c]						
24–39	113	13	204	22	317	17
40–44	121	13	141	15	262	14
45–49	206	23	174	19	380	21
50–54	195	22	177	19	372	20
55–59	152	17	129	14	281	15
60–71	115	13	111	12	226	12
Race/ethnicity						
White	813	90	830	89	1643	89
Black	14	2	7	1	21	1
Hispanic	24	3	35	4	59	3
Asian/PI	29	3	36	4	65	4
Other	22	2	28	3	50	3
Study collection site						
Cancer Prevention Institute of California	437	48	467	50	904	49
City of Hope	277	31	282	30	559	31
University of California Irvine	188	21	187	20	375	20
Family history of breast cancer (first degree relative)[c]						
No	729	81	805	86	1534	83
Yes	136	15	102	11	238	13
Unknown	37	4	29	3	66	4
BMI (kg/m^2) [c]						
16.0–24.9	497	55	581	62	1078	59
25.0–29.9	236	26	213	23	449	24
30.0–54.8	153	17	117	13	270	15
Outlier/unknown	16	2	25	3	41	2
Long-term strenuous & moderate physical activity (hours/week)[c,d]						
≥4.00	275	30	312	33	587	32
0.50–3.99	257	28	311	33	568	31
< 0.50	369	41	310	33	679	37
Unknown	1	0	3	0	4	0
Parity/age at first full-term pregnancy (years)						
Nulliparous	234	26	226	24	460	25
≤24 years	206	23	246	26	452	25
25–29 years	259	29	269	29	528	29
≥30 years	193	21	180	19	373	20
Unknown	10	1	15	2	25	1
Dietary pork consumption[c]						
None	354	39	413	44	767	42
< Median	243	27	279	30	522	28
≥Median	235	26	190	20	425	23
Unknown	70	8	54	6	124	7
Menopausal status/hormone therapy (HT) use at blood draw[c]						
Pre- or peri-menopausal	43	5	104	11	147	8
Post-menopausal and never used HT	286	32	269	29	555	30
Post-menopausal and ever used HT	573	64	562	60	1135	62
Unknown menopausal status	0	0	1	0	1	0
Season of blood draw[c]						
Winter	213	24	317	34	530	29
Spring	275	30	220	24	495	27
Summer	242	27	170	18	412	22
Fall	172	19	229	24	401	22
Date of blood draw[c]	902	Ave.: 5/01/13 Min:11/22/11 Max: 8/24/15	936	Ave.:6/05/13 Min:11/01/11 Max: 8/24/15	1838	Ave.: 5/19/13 Min: 1/01/11 Max: 8/24/15

[a] Includes all characteristics that were included as covariates in the fully-adjusted multivariable logistic regression models.
[b] Characteristic assessed at CTS baseline enrollment, unless otherwise noted.
[c] Distributions for cases and controls were statistically different (i.e., p (chisq) < 0.05).
[d] Long-term physical activity includes activity from high-school through current age or age 54 if 55 years of age or older.

study. Compared to controls, cases were significantly more likely to be older and post-menopausal. Cases also were significantly more likely than controls to report a family history of breast cancer, have higher BMI, report less physical activity, and consume more pork. Controls were significantly more likely than cases to have had their blood sample collected during the initial few months of the study and during the fall and winter months (Table 1). All factors as specified in Table 1 were included as covariates in our logistic regression analyses.

Consistent with national biomonitoring data (Centers for Disease Control and Prevention, 2015), lipid-normalized serum concentrations were highest for BDE-47, followed by BDE-153, and BDE-100 (geometric means = 14.1 ng/g, 5.3 ng/g, and 2.6 ng/g, respectively). Statistically significant positive correlations ($p < 0.001$) were observed between all congeners. Serum levels of BDE-100 and BDE-47 were highly correlated ($r = 0.89$) while BDE-153 was less strongly correlated with the other congeners ($r = 0.54$ for BDE-100; $r = 0.36$ for BDE-47). Serum PBDE and lipid concentrations for cases and controls are presented in Table 2. Median concentrations of the BDE congeners did not statistically differ between cases and controls. Total Lipids were

Table 2
Serum concentration of PBDEs and total lipids among 902 breast cancer cases and 936 controls.[a]

	DF[d]	LOD[e]	Serum concentration[b,c]				
			Mean	Median	Minimum	Maximum	p-Value[f]
BDE-47							
Cases	85.9	0.033	0.139	0.080	0.003	1.706	
Controls	87.0	0.033	0.167	0.086	0.005	3.665	0.22
BDE-100							
Cases	74.4	0.008	0.030	0.015	0.0003	0.873	
Controls	76.4	0.008	0.034	0.016	0.001	0.841	0.39
BDE-153							
Cases	75.5	0.017	0.074	0.030	0.001	2.233	
Controls	78.0	0.017	0.080	0.032	0.001	2.905	0.54
Total lipids							
Cases	–	–	6.43	6.26	3.86	12.62	
Controls	–	–	6.54	6.46	3.18	11.48	0.01

[a] Data presented only for the BDE congeners with detection frequencies (DF) ≥ 75%.
[b] Concentration expressed in ng/mL for BDE congeners and mg/mL for total lipids.
[c] Distributions for the BDE congeners based on measured and imputed values where samples below the limit of detection (LOD) were estimated by single imputation from a log-normal probability, based on method suggested by Lubin et al. (2004).
[d] DF = detection frequency for BDE congener.
[e] LOD = average limit of detection for BDE congener.
[f] p-Value from the Wilcoxon rank sum test for differences in medians by case-control status.

Table 3
Association of invasive breast cancer risk with serum PBDE concentrations among 1838 study participants.

PBDE serum concentration	# cases	# controls	Crude[a,b] OR (95% CI)	p-Value[c]	Fully adjusted[a,d] OR (95% CI)	p-Value[c]
BDE-47						
Q1 (lowest quartile)	240	237	1.00 (ref)	0.47	1.00 (ref)	0.28
Q2	234	231	1.03 (0.80, 1.34)		1.11 (0.85, 1.45)	
Q3	218	234	0.93 (0.71, 1.21)		0.97 (0.74, 1.28)	
Q4 (highest quartile)	210	234	0.93 (0.72, 1.22)		0.88 (0.67, 1.17)	
log [BDE-47, ng/mL]	902	936	0.90 (0.72, 1.13)	0.37	0.84 (0.66, 1.07)	0.15
BDE-100						
Q1 (lowest quartile)	240	231	1.00 (ref)	0.53	1.00 (ref)	0.29
Q2	231	237	0.95 (0.73, 1.23)		0.97 (0.75, 1.28)	
Q3	212	233	0.89 (0.68, 1.15)		0.87 (0.66, 1.15)	
Q4 (highest quartile)	219	235	0.94 (0.72, 1.22)		0.89 (0.67, 1.17)	
log [BDE-100, ng/mL]	902	936	0.93 (0.76, 1.14)	0.48	0.87 (0.71, 1.08)	0.21
BDE-153						
Q1 (lowest quartile)	232	227	1.00 (ref)	0.52	1.00 (ref)	0.65
Q2	236	240	1.03 (0.80, 1.34)		1.00 (0.77, 1.32)	
Q3	240	235	1.09 (0.84, 1.41)		1.13 (0.86, 1.49)	
Q4 (highest quartile)	194	234	0.89 (0.68, 1.17)		0.89 (0.67, 1.18)	
log [BDE-153, ng/mL]	902	936	0.95 (0.78, 1.15)	0.57	0.93 (0.77, 1.14)	0.50

[a] OR = odds ratio; CI = confidence interval.
[b] Crude ORs adjusted for matching design variables of age at baseline enrollment, race/ethnicity, study collection site, and total serum lipids.
[c] For the categorical analysis, the *p*-values represent a test for linear trend with quartiles of PBDE modeled as a 4-level ordinal variable; for the continuous BDE term, the *p*-value represents the p-value of the Wald-statistic for the b-coefficient for the BDE congener modeled as a continuous term.
[d] Fully adjusted ORs adjusted for age at baseline enrollment, race/ethnicity, study collection site, total serum lipids, date of blood draw, season of blood draw, body mass index, physical activity, family history of breast cancer, parity/age at first full-term pregnancy, menopausal status/hormone therapy use at blood draw, and pork consumption.

marginally higher in controls compared to cases ($p < 0.01$), a difference that was driven by higher levels of cholesterol (median in controls = 203.0 mg/dL versus in cases = 194.0 mg/dL, $p < 0.01$) but not in triglycerides (median in controls = 112.0 mg/dL versus in cases = 115.0 mg/dL, $p = 0.36$)

The ORs for breast cancer associated with serum concentrations of PBDEs from the crude and fully-adjusted multivariable logistic regressions are presented in Table 3.

No statistically significant associations were observed for any of the three congeners, regardless of whether the serum concentrations were modeled as continuous or as ordinal terms. All ORs were close to 1.0 and 95% confidence intervals included 1.0. Estimates generated from the crude and fully-adjusted models did not substantially differ. Stratification of the data by menopausal status yielded risk estimates for the post-menopausal women similar to those for the full study population and no statistically significant effects were observed (Supplemental Table S2). While the pattern of risk appeared somewhat different among the small number of women ($n = 147$) who were pre- or peri-menopausal, none of the ORs significantly differed from one. Likewise, stratification by tumor hormone responsiveness did not reveal any statistically significant associations between PBDEs and breast cancer risk (Supplemental Table S3). With few exceptions, stratification by categories of BMI and changes in body weight generally yielded similarly null results (Supplemental Tables S4 and S5). Analyses within additional subsets of the study population (including parous women who had breastfed, women who had never used menopausal hormone therapy, and among women who entered menopause or experienced their first full-term pregnancy during peak human population exposures) demonstrated similar patterns of risk and did not yield statistically significant findings (*data not shown*).

Among the cases, we observed no evidence that serum PBDE concentrations varied by the time interval between diagnosis and blood draw. There was no correlation between PBDE serum levels and the time interval between diagnosis and blood draw (Spearman Rank correlations ranged from −0.1 to 0.05 and none were statistically significant). Moreover, stratified risk analyses indicated a similar pattern of null results among both cases that had their blood drawn within three years and those who had it drawn more than three years since diagnosis.

4. Discussion

The results of this case-control study provide no evidence that serum concentrations of BDE-47, BDE-100 or BDE-153 are associated with breast cancer risk in this population of middle-aged and older California women where cases' samples were collected several months to several years after breast cancer diagnosis and treatment. All odds ratio estimates were close to one with confidence intervals that included one. While our subset analyses yielded a few statistically-significant findings, these results were sensitive to whether the PBDE was modeled as a continuous or an ordinal variable and showed no evidence of dose-response. We therefore regard these few statistically significant results as spurious findings, especially in light of the numerous subset analyses that were conducted.

These results add to a small body of research on this topic. Only two prior epidemiologic studies have evaluated the association between body burden measurements of PBDEs and breast cancer risk, both of which also reported null results (Holmes et al., 2014; Hurley et al., 2011). One of these studies was conducted among women who were demographically similar to those we studied–as it included women who were mostly well-educated middle/upper-class non-Hispanic whites living in the greater San Francisco Bay Area (SFBA) of California (Hurley et al., 2011). The other study was conducted among Native Alaskan women and reported a statistically significant unadjusted OR for BDE-47 which did not persist after multivariable adjustment (Holmes et al., 2014). These two prior case-control studies, each comprised of fewer than 80 cases, had limited statistical power to detect risks. Furthermore, as hospital-based studies in which cases and controls were both identified from pools of patients presenting for breast surgeries (including biopsies, lumpectomies, mastectomies, or breast reconstructions), these studies may have suffered from over-matching. As the largest study conducted to date, our case-control study, nested within a well-specified cohort, was better-positioned than prior studies to explore associations between PBDEs and breast cancer risk. Nevertheless, several potential limitations are worth noting as they may have impeded our ability to detect an association where one may have

existed.

The most important potential limitation to our study is that our cases' PBDE measurements were from blood collected an average of 35 months after diagnosis and after treatment. While it was not possible to directly ascertain the degree to which this may have influenced our results, our efforts to indirectly assess this issue through a number of sensitivity analyses did not reveal any evidence that PBDE levels in cases varied by how much time had elapsed between diagnosis and blood sample collection. To our knowledge, no data have been published on how PBDE serum levels may be affected by the onset of breast cancer or influenced by its treatment. However, a few small exploratory studies have evaluated this issue for other lipophilic POPs and these may offer some insight. A breast cancer study that had serial measures of organochlorine compounds in serum taken over the course of two-years (including at least 6 months prior to diagnosis in cases) reported similar declines in cases and controls, suggesting that the onset of disease did not affect serum levels (Wolff et al., 2000a). That study however was not able to account for treatment. One study of PCB serum levels (Gammon et al., 1996) and another of breast cancer risk (Gatto et al., 2007) suggested that both levels and risk may be modified by chemotherapy. While these studies highlight the potential importance of treatment effects, this issue remains poorly understood and represents an area worthy of future research. Unfortunately, we do have not complete information on treatment for our study participants. Cancer treatment data for the CTS, derived from the CCR, consists of information on first course of treatment and therefore does not capture all therapies provided by adjuvant care. It is noteworthy, however, that the two prior breast cancer case-control studies, which were also null, were both based on biospecimens collected before treatment (Holmes et al., 2014; Hurley et al., 2011).

The use of a single serum measurement has generally been accepted as a reasonable proxy for chronic exposure levels of other POP compounds in healthy individuals, based on a number of analyses that have shown strong intra-individual correlations between serial measurements taken over time and a constancy of the relative exposure rankings (i.e., high/medium/low) across individuals over time (Gammon et al., 1997; Vo et al., 2008; Wolff et al., 2000b). The degree to which this supposition extends to the PBDEs, which have shorter half-lives than many of the legacy POPs, is not known. PBDE exposures, however, are ubiquitous and on-going. Thus, while a single serum measurement later in life, such as was used in this study, may not be a precise estimate of exposure for an earlier more etiologically-relevant time period, it likely provides a reasonable characterization of relative ranking among study participants. There are, however, several additional caveats related to this issue worth noting that may be especially germane to breast cancer studies. In particular, intra-individual changes in POPs body burden levels may vary substantially by lactation history and BMI (Vo et al., 2008; Wolff et al., 2000b; Chevrier et al., 2000; Rogan, 1996; Sasamoto et al., 2006; Sweeney et al., 2001; Wolff et al., 2005), which are also recognized risk factors for breast cancer. In our study, lactation history was not associated with PBDE levels and analyses limited to those who had never breastfed did not yield results that differed substantially from those based on all women (*data not shown*). BMI, however, was a significant confounder and our BMI-stratified analyses suggested a reduced risk for BDE-47 only among obese women (Supplemental Table S4). In light of the many subset analyses that were conducted, and given that this finding was sensitive to whether BDE-47 was specified as an ordinal or continuous term, we tend to regard it as spurious. It is possible however that it could be an artifact of the degree to which a single serum measurement taken later in life (and after diagnosis among cases) may differentially capture chronic exposures among women with varying BMI. Alternatively, it is possible this finding is reflective of toxicokinetic mechanisms that are influenced by body weight, percentage of body fat, or type of body fat– a supposition supported by compelling evidence summarized in a recent review of the role of adipose tissue in modulating POPs toxicity (La Merrill et al., 2013).

In addition to BMI, changes in body weight also appear to be important determinants of serum POPs concentrations (Chevrier et al., 2000; Sweeney et al., 2001; Wolff et al., 2005; La Merrill et al., 2013; Verner et al., 2008; Wolff et al., 2007). This is of concern because changes in body weight, particularly weight gain, are common among breast cancer patients, especially among those who receive chemotherapy (Makari-Judson et al., 2007; Vance et al., 2011). Our ability to fully consider changes in BMI was limited by the availability of serially-collected BMI data at relevant points in time. Specifically, we did not have updated BMI information at the time of blood collection but rather had to rely on BMI information collected in 2011–2012 (which ranged from as much as 4 years prior to within a year after blood collection). Based on these data (which would not necessarily capture changes in body weight related to diagnosis or treatment), we generally did not observe differences in PBDE risks among women who did and did not have substantial changes in body weight (Supplemental Table S5).

Beyond the concern of whether the use of a single serum measurement adequately serves as a valid proxy for chronic PBDE exposures, another concern is that earlier exposures during potentially important windows of susceptibility may not have been captured (Gray et al., 2017; Institute of Medicine of the National Academies, 2014; Mouly and Toms, 2016; Rodgers et al., 2018). Our attempts to indirectly address this issue by doing some focused analyses for participants who may have had the greatest opportunity of exposure by virtue of having been pregnant or undergone menopause during the peak windows of population exposures did not prove illustrative (*data not shown*). If risks are only posed by exposures during perinatal or pubertal development, the vast majority of our participants would not have been at risk as 75% were born before 1952 and all were born before 1972 – prior to the widespread use of these chemicals.

5. Conclusion

In summary, the results from this study add to a small body of epidemiologic evidence that suggests PBDE exposures captured at middle age or older are not related to breast cancer risk. While our large study had substantially greater statistical power to detect effects than the prior two studies, it shares with those studies the primary limitation of reliance upon biomarkers of exposure that may not provide adequate estimates of chronic or early-life exposures. Furthermore, in our study we could not consider a number of factors that may be important modifiers of risks associated with these compounds, including polymorphisms in Cytochrome p450 genes and other factors such as body fat that may affect endogenous estrogen levels.

Given the few epidemiologic studies conducted to date, none of which have been able to adequately address these methodologic limitations, it would be premature to conclude that PBDEs pose no risk for breast cancer. Further laboratory and epidemiologic investigations that can better address these outstanding issues are warranted given the ubiquitous human exposures to these compounds that are expected to persist for many decades.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.03.043.

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