Exposure to Polybrominated Diphenyl Ethers and a Polybrominated Biphenyl and Risk of Thyroid Cancer in Women: Single and Multi-Pollutant Approaches

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Abstract

Background: Thyroid cancer incidence is the most rapidly increasing malignancy; rates are three times higher in women than men. Thyroid hormone–disrupting flame-retardant chemicals, including polybrominated diphenyl ethers (PBDE) and polybrominated biphenyls (PBB), may contribute to this trend.

Methods: We investigated the relationship between PBDE/PBB exposure and papillary thyroid cancer (PTC) in 250 incident female papillary thyroid cancer cases and 250 female controls frequency-matched on age. Interviews and postdiagnostic serum samples were collected from 2010 to 2013. Serum samples were analyzed for 11 congeners. We calculated ORs and 95% confidence intervals (95% CI) using single-pollutant logistic regression models for continuous and categorical lipid-adjusted serum concentrations of PBDE/PBB, adjusted for age, alcohol consumption, and education. We applied three multi-pollutant approaches [standard multi-pollutant regression models, hierarchical Bayesian logistic

regression modeling (HBLR), principal components analysis (PCA)] to investigate associations with PBDE/PBB mixtures.

Results: In single-pollutant models, a decreased risk was observed at the highest (>90th percentile) versus lowest (<median) category of BDE-209 concentrations (OR, 0.47; 95% CI, 0.23–0.98); an elevated PTC risk was observed at the highest versus lowest category of BB-153 concentrations (OR, 1.81; 95% CI, 0.96–3.39). In standard multi-pollutant models, an interquartile range increase in BDE-100 concentrations was associated with increased PTC risk (OR, 1.18; 95% CI, 1.01–1.38). HBLR and PCA yielded no statistically significant results.

Conclusions: Our results using single- and multi-pollutant modeling do not generally support a positive association with PBDE/PBB and PTC risk.

Impact: Prospective studies with more advanced statistical approaches to analyze mixtures and populations with higher exposures could reveal new insights.

Introduction

Thyroid cancer rates have been increasing rapidly worldwide for the past decades; in the United States, age-adjusted thyroid cancer incidence rates have increased 3-fold from 4.8 cases/100,000 in 1975 to 15.0/100,000 in 2015 such that approximately 1.2% of adults will be diagnosed with thyroid cancer in their lifetime (1, 2). Incidence rates in women are three times those in

men (3, 4). Papillary thyroid cancer (PTC) is the most common subtype, comprising approximately 80% of new cases (5).

The increasing trend can be partially explained by improved diagnostic imaging methods, such as ultrasounds, positron emission tomography, and CT, which more accurately detect small thyroid nodules for early medical attention (6). However, this is unlikely to be the sole driver, as incidence rates are also increasing for more easily detectable larger tumors and among younger individuals less likely to be targeted for screening (7, 8). Some risk factors for thyroid cancer have been identified, such as ionizing radiation exposure, family history, reduced or excess iodine consumption, and obesity (6, 9); however, the etiology generally remains poorly understood. Exposures to thyroid hormone–disrupting environmental chemicals have been suggested as another potential risk factor (10, 11).

Polybrominated diphenyl ethers (PBDE) are flame retardants used in commercial and household products such as plastics, electronics, foam furniture padding, and upholstery (12, 13). PBDE are not chemically bound to their products and therefore can leach into the environment, partitioning into dust particles and other media, where they can accumulate overtime (13–15). Human exposures to these compounds increased 1–2 orders of magnitude from the mid-1970s to mid-2000s (14, 16). Studies had initially reported subsequent declines in serum concentrations of several PBDE in the United States and other nations due to

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manufacturing restrictions resulting from concern about widespread exposure, persistence, and potential toxicities (17, 18); however, recent publications indicate that serum concentrations of several congeners have plateaued or increased from 2011 to 2015 (19, 20), indicating continued exposure. Furthermore, these compounds remain ubiquitous in currently available consumer products, the environment, the food supply, and the human body due to their stability and lipophilicity (21–23). Exposures may also remain elevated in certain developing countries, where regulations pertaining to production and use are less stringent (24). Polybrominated biphenyls (PBB), structurally similar flame retardants, were added to plastics used in a variety of household products in the United States until 1976 (25). Decades later, PBB exposure remains common throughout the United States (26).

Several mechanisms of thyroid carcinogenicity have been proposed. PBDE have been demonstrated to disrupt thyroid hormone homeostasis in animals and humans (27). Because they are structurally analogous to thyroid hormones triiodothyronine (T3) and thyroxine (T4), PBDE and their hydroxylated metabolites may competitively bind with thyroid hormone transport proteins, resulting in reduced circulation of thyroid hormones. This has been hypothesized to cause abnormal proliferation in the thyroid, which may result in tumorigenesis (10). Other research has shown that PBDE hydroquinone metabolites are capable of forming DNA adducts (28, 29), possibly leading to mutations or chromosomal aberrations, which could result in carcinogenicity. Another possible mechanism is PBDE-mediated upregulation of cytochrome-P450 enzymes, which generate more reactive oxygen species and oxidative stress, which in turn may promote tumor development and progression (30). PBBs have been linked to thyroid hormone disruption via similar mechanisms (30–33).

In toxicology studies, increased thyroid follicular adenomas have been observed in rats exposed to commercial flame-retardant mixtures including deca-BDE (consisting primarily of the congener BDE-209; ref. 34) and penta-BDE (consisting primarily of BDE-99, BDE-47, BDE-100, BDE-153, and BDE-154; ref. 30). PBB have been linked to carcinogenic effects in male and female rats and mice, particularly hepatocellular carcinomas (33, 35).

There is a paucity of epidemiologic evidence on the relationship between PBDE exposure and risk of thyroid cancer, with only two published studies on this topic, to our knowledge. A nested case–control study carried out in multiple locations in the United States found no significant association between serum levels of four PBDE congeners (BDE-47, BDE-99, BDE-100, and BDE-153) and increased risk of PTC (36). As noted by the authors, this analysis had a few important limitations, including relatively low case numbers (104 cases, 208 controls), a population generally older than peak age of diagnosis (median age of 62 years), and few congeners with sufficient detection frequencies for analysis. A case–control study in North Carolina that measured PBDE in both serum and house dust (37) observed statistically significant higher odds of PTC among those with house dust BDE-209 concentrations greater than the median compared with below, particularly for smaller tumors (<2 cm). No associations were observed for serum concentrations of the two congeners with sufficient detection frequency for analysis (BDE-47 and BDE-153). This study also had small case numbers (70 cases, 70 controls). Although the authors applied a principal components analysis to examine effects of joint exposures, this was constrained

by the small sample size and did not reveal any new information. To our knowledge, no epidemiologic studies of PBB exposure and thyroid cancer have been conducted.

The objective of the current case–control study is to examine the association of PBDE/PBB serum levels and risk of PTC in Connecticut women with a larger number of cases and numerous congeners using single-pollutant and multi-pollutant approaches. This represents the largest study to date and the first study to present results for the relationship between individual and joint exposures to several PBDE and thyroid cancer.

Materials and Methods

Study population

This analysis was conducted within a previously described population-based case–control study of thyroid cancer in Connecticut (38, 39). Briefly, eligible cases were those aged 21 to 84 years at diagnosis with no previous cancer diagnosis except nonmelanoma skin cancer. Histologically confirmed (papillary, follicular, medullary, and anaplastic) incident thyroid cancer cases diagnosed between 2010 and 2011 were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource, part of Connecticut Tumor Registry. A total of 462 cases participated (65.9% participation rate). Controls were Connecticut residents identified through random digit dialing (61.5% participation rate) and frequency-matched to cases by age (±5 yr). We necessarily conducted our analysis on a subset of the parent study population due to resource constraints. We focused on female Caucasians, as they were more likely to be cases compared with individuals of differing demographics. In the parent study, cases were 81% female and 90% White (39). Therefore, we conducted the current analysis in 250 randomly selected female Caucasian cases of PTC and 250 female Caucasian controls.

Collection of personal data, covariates, and potential confounders

Procedures were performed in accordance with protocols approved by the Human Investigation Committees at Yale University and Connecticut Department of Public Health; the Centers for Disease Control and Prevention (CDC) determined that the agency was not engaged in human subjects' research. All participants provided informed written consent. In-person interviews were conducted in participant homes by trained interviewers using a standardized, structured questionnaire including questions about demographic characteristics, radiation exposure, smoking and alcohol use, medical history, lifetime occupational history, and lifetime residential history.

Serum collection and analysis

Blood samples were collected by a trained phlebotomist at the in-person interviews. Most cases had their serum sampled within 6 months of diagnosis [median: 174 days, interquartile range (IQR): 121–238 days]. After separation from whole blood, serum samples were aliquoted and stored at −20°C until shipment to the CDC (Atlanta, GA) for analysis. Samples were analyzed for ten PBDE congeners and one PBB congener: BDE-17, BDE-28, BDE-47, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-209, BB-153, using gas chromatography isotope dilution high resolution mass spectrometry (GC-IDHRMS) employing a DFS instrument (Thermo DFS); the analytic method has been described in detail (40, 41). Total serum lipid concentrations were

measured to normalize the concentrations of PBDE in serum, quantified using commercially available enzymatic methods (Roche Diagnostics Corp) for total triglycerides and total cholesterol on a Hitachi 912 Chemistry Analyzer (Hitachi). All concentration data were reported as ng/g lipid weight and were background-corrected by subtracting the average concentration in blank samples (42). Three blanks and three quality control/quality assurance samples prepared internally by the laboratory were included in every set of 30 samples; in addition, 25 laboratory-blind quality control (QC) samples were included across the batches. Laboratory personnel were blinded to case–control status. The coefficient of variation (CV) from laboratory-blind QCs ($n = 25$) ranged from 2.76% (BDE-99) to 7.23% (BDE-85), indicating a high level of reproducibility.

Statistical analysis

Seven congeners (BDE-28, 47, 99, 100, 153, 209, BB-153) were measured in >80% of samples; concentrations were right-skewed. For these compounds, we used a single imputation method to assign a value to samples below the method detection limit (DL) using a maximum likelihood procedure that assumed a lognormal distribution defined by the distribution of measurements above the DL (43); no covariates were used in the imputation process. The use of a single imputation generally yields unbiased risk estimates and accurate measures of variance when the percent missing is ≤30% (43). In our analyses of these highly detected compounds, we examined both the continuous PBDE concentrations and categories of PBDE concentrations based on distributions among controls. All continuous PBDE concentrations were standardized for regression analyses by subtracting the mean and dividing by the SD to reduce the influence of outliers and to improve computational stability during model fitting. This achieves the same benefits as the more commonly used natural log transformation while retaining interpretability on the arithmetic scale. To address the low variability in PBDE/PBB serum concentrations across the population, we assigned categories corresponding to ≤ median, >median and ≤90th percentile, and >90th percentile.

Three congeners (BDE-85, 154, 183) had detection frequencies of approximately 30% and were therefore modeled as detected versus nondetected; continuous concentrations were not modeled. PBDE-17 was detected in only 3.6% of the samples and therefore was excluded from statistical analyses.

In traditional, single-pollutant models, ORs and 95% confidence intervals (95% CI) were calculated using logistic regression in separate models for each congener. We considered the following variables as potential confounders of the association of serum PBDE levels and risk of PTC based on a review of the literature: frequency of dental X-ray exposure (never to more than once/year), diagnostic X-ray exposure (ever have diagnostic X-rays such as chest X-rays or mammograms), tobacco use (ever smoked ≥100 cigarettes), alcohol use (ever consumed ≥12 servings of alcoholic beverages), family history of cancer among first-degree relatives, educational attainment, family income per capita, age, and body mass index (BMI). All potential confounders were included in the logistic regression models for each congener and removed via backward elimination if their removal yielded a ≥10% change in the OR. Years of education, age, and alcohol consumption met inclusion criteria in most models and therefore we included them in all final models. We conducted stratified analyses to examine whether there was any difference in relation-

Table 1. Distribution of selected characteristics of the PTC cases and controls

	Cases (n = 250)	Controls (n = 250)	P^a
Age			0.10
<40	51	34	
40–49	69	76	
50–59	78	72	
60–69	40	45	
≥70	12	23	
Years of education			0.02
High school or less	72	41	
Technical school	14	14	
College	99	123	
Graduate/professional school	54	66	
Other	9	5	
Poverty level			0.14
Below poverty level	10	2	
Above poverty level	173	171	
Unknown	69	75	
Family income			0.65
<24,999	17	20	
25,000–49,999	29	23	
50,000–89,999	45	37	
>90,000	90	95	
Refused	66	74	
Missing	3	1	
BMI			0.06
<25	90	111	
25–29.99	75	76	
≥30	85	63	
Family history of cancer			0.05
No	76	77	
Thyroid cancer	42	24	
Other cancer	132	149	
Thyroid disease			<0.0001
Yes	38	4	
No	212	246	
Smoking			0.34
Yes	75	85	
No	175	165	
Alcohol consumption			0.001
Yes	95	127	
No	155	123	
Dental X-rays			0.37
Never	9	5	
Less than every few years	90	105	
Every few years	35	41	
Once a year	97	89	
More than once a year	14	8	
Unknown	5	2	
Prior diagnostic medical radiation exposure			0.35
Yes	233	233	
No	17	15	
Unknown	0	2	
Tumor diameter			–
≤1 cm	140	–	
>1 cm	110	–	

$^a P$ value corresponds to χ^2 test.

ships between PBDE exposure and PTC based on tumor size using two size cut-off points: tumors with diameter ≤ 1 cm (microcarcinoma) and >1 cm and tumors ≤2 cm and > 2 cm. Papillary microcarcinoma are generally considered of lower clinical significance, because they often remain indolent and have a positive prognosis (44). However, some microcarcinoma have been reported to have aggressive and metastatic behavior (45). A cut-off point of 2 cm was also examined because of its application in the assessment of clinical or pathologic stage.

We applied three multi-pollutant methods to examine the association between concurrent exposures to multiple PBDE/PBB and risk of PTC. First, we used a multiple logistic regression to jointly analyze the impact of all 10 congeners within a single model. A traditional multiple regression model, including all individual congeners, is preferable to the common practice of summing all congeners for several reasons. First, the sum is often highly correlated with the pollutant present at the highest concentration and therefore is merely a proxy for the dominant chemical. Second, signals may be masked if effects of individual chemicals trend in different directions, as commonly occurs with endocrine-disrupting chemicals (46). Third, different studies measure different congeners, and therefore the sum may not be comparable across publications. However, a multiple logistic regression model with all 10 congeners may be unstable due to high correlations between certain congeners (e.g., $r_{Spearman} = 0.95$ between PBDE 47 and PBDE 99; Supplementary Table S1), leading to inflated standard errors and potentially misleading risk parameter estimates.

Second, we applied a hierarchical Bayesian statistical approach similar to method "P2" presented in ref. 47. In this method, the regression parameters corresponding to the different congeners are assumed to follow a normal distribution, centered at zero, with a common variance parameter (to be estimated). By incorporating this prior distribution structure, we carried out data-driven shrinkage of the individual risk parameters toward zero, thereby leading to more stable parameter estimates and statistical inference that may be less impacted by the high correlations between exposures. Full details are presented in the Supplementary Material.

Finally, we applied a principal component analysis (PCA) on the raw PBDE concentrations paired with a logistic regression analysis to investigate possible interactive effects between multiple chemicals. Using the factor loadings, we created new exposure metrics that represent linear combinations of individual congeners. On the basis of the Kaiser rule [i.e., only keeping the principal components (PC) with eigenvalues of at least one (48)], we identified the most important PCs and investigated their association with cancer risk using a multiple logistic regression analysis.

As a sensitivity analysis, we refit each of these multipollutant methods to the subset of cases with and without microcarcinoma separately to determine the impact of tumor size on associations with exposure. Single-pollutant modeling was done with SAS (Version 8.4, SAS Institute Inc.) and multi-pollutant methods were applied within the R statistical software package (R Foundation for Statistical Computing; https://www.R-project.org/). All multi-pollutant models were adjusted for the same covariates as the single-pollutant models.

Results

Compared with controls, cases tended to be younger, less educated, have higher BMI, be less likely to consume alcohol, and be more likely to have a family history of thyroid cancer ($P \leq 0.1$; Table 1). Cases and controls were similar with respect to income, smoking status, receipt of dental X-rays, and diagnostic medical radiation.

The distributions of the lipid-adjusted concentrations of the different congeners in serum for cases and controls are presented in Table 2. BDE-47 was present at the highest concentrations, with a median (IQR) lipid-adjusted concentration among controls of 7.28 ng/g lipid (4.04–15.33), followed by BDE-153 [3.08 ng/g lipid (2.02–5.86)], BDE-209 [1.55 ng/g lipid (1.00–2.41)], BB-153 [1.45 ng/g lipid (1.00–2.41)], BDE-100 [1.47 ng/g lipid (0.78/2.86)], and BDE-99 [1.21 (0.66–2.74)]. Median concentrations of BDE-17, BDE-28, BDE-85, and BDE-183 were all <1 ng/g lipid. Concentrations in cases were similar or lower than in controls. Comparison of the 25th and 75th percentiles indicates that the variability in congener exposures was relatively small.

Spearman correlation coefficients ($r_{Spearman}$) between PBDE concentrations ranged from −0.09 to 0.95 with a median of 0.20 (Supplementary Table S1). Stronger correlations were observed between congeners with similar degrees of bromination or PBDE present in the same commercial products. For example, the following six pairs of congeners had Spearman correlation coefficients >0.8: BDE-28 and BDE-47 ($r_{Spearman} = 0.92$), BDE-28 and BDE-99 ($r_{Spearman} = 0.83$), BDE-28 and BDE-100 ($r_{Spearman} = 0.85$), BDE-47 and BDE-99 ($r_{Spearman} = 0.95$), BDE-47 and BDE-100 ($r_{Spearman} = 0.92$), BDE-99 and BDE-100 ($r_{Spearman} = 0.88$).

Table 2. Distributions of serum concentrations of PBDE flame retardants in female PTC cases and controls

| | | | | Serum concentrations (ng/g lipid) | | | |
| | | | | Cases (*n* = 250) | | Controls (*n* = 250) | |
Chemical name (abbreviation)	Estimated half-life (yr)[a]	Median LOD	% > LOD	Median	25th–75th percentile	Median	25th–75th percentile
2,2′,4-Tribromodiphenyl ether (BDE-17)	NI	0.17	4	<LOD[b]	<LOD[b]	<LOD[b]	<LOD[b]
2,4,4′-Tribromodiphenyl ether (BDE-28)	3.0	0.20	82	0.44	0.22–0.73	0.51	0.26–1.0
2,2′,4,4′-Tetrabromodiphenyl ether (BDE-47)	1.4–3.0	0.39	99	6.36	3.45–10.94	7.28	4.04–15.33
2,2′,3,4,4′-Pentabromodiphenyl ether (BDE-85)	NI	0.18	33	<LOD[a]	<LOD[a]	<LOD[a]	<LOD[a]
2,2′,4,4′,5-Pentabromodiphenyl ether (BDE-99)	5.4	0.22	95	1.04	0.54–1.74	1.21	0.66–2.74
2,2′,4,4′,6-Pentabromodiphenyl ether (BDE-100)	1.8–2.9	0.17	98	1.27	0.69–2.33	1.47	0.78–2.86
2,2′,4,4′,5,5′-Hexabromodiphenyl ether (BDE-153)	7.4–11.7	0.17	100	3.04	1.77–6.01	3.08	2.02–5.86
2,2′,4,4′,5,6′-Hexabromodiphenyl ether (BDE-154)	5.8	0.16	37	<LOD[a]	<LOD[a]	<LOD[a]	<LOD[a]
2,2′,3,4,4′,5′,6-Heptabromodiphenyl ether (BDE-183)	0.26–0.30	0.16	28	<LOD[a]	<LOD[a]	<LOD[a]	<LOD[a]
Decabromodiphenyl ether (BDE-209)	0.04–0.07	0.83	84	1.47	1.04–2.14	1.55	1.00–2.41
2,2′,4,4′,5,5′-Hexabromobiphenyl (BB-153)	13–29	0.17	97	1.40	0.82–2.33	1.45	0.94–2.44

Abbreviation: LOD, limit of detection.

[a]Half-lives compiled from Geyer et al. 2004 (50), McDonald et al. 2005 (62), Thuresson et al. 2006 (51), Blanck et al. 2000 (63). NI indicates a half-life was not identified for that congener in the literature.

[b]Median and quartile limits not calculated because <60% detection frequency for this compound.

The commercial mixture penta-PBDE is comprised primarily of BDE-47 and BDE-99.

In adjusted single-pollutant models, BB-153 had an elevated but nonstatistically significant association with PTC risk when comparing the highest exposure category (>90th percentile) to the reference (≤median; OR: 1.81; 95% CI: 0.96–3.39; Table 3). A decreased risk was observed at the highest category of BDE-209 exposure (>90th percentile) compared with the reference (≤median; OR: 0.47; 95% CI: 0.23–0.98). No other statistically significant associations were observed. Results stratified by tumor sizes demonstrated statistically significantly inverse associations with risk of microcarcinomas for six PBDE congeners (generally when comparing the highest exposure category to the reference), while effect sizes were near one for the larger tumor sizes (Table 4). Results stratified by tumor sizes using the 2-cm cut-off point were similar to those for the microcarcinoma, yielding no statistically significant associations for the larger tumors and some statistically significant inverse associations for the smaller tumors (Supplementary Table S2). However, some of the effect estimates for tumors >2 cm were elevated compared with those for tumors >1 cm.

Multiple logistic regression analysis risk parameter estimates (OR scale) and confidence/credible intervals from the standard regression model including all continuously modeled PBDE/PBB and the hierarchical Bayesian method are presented in Fig. 1. A statistically significant positive association was observed between BDE-100 and thyroid cancer risk (OR per interquartile range increase in exposure: 1.18; 95% CI: 1.01–1.38; P: 0.04). However, this finding is inconsistent with the single-pollutant, the hierarchical Bayesian, and the PCA modeling results.

No statistically significant associations were observed in the Bayesian modeling. The shrinkage that results from the hierarchical Bayesian method can be clearly observed as the credible intervals are much narrower than the corresponding CIs from the standard multi-pollutant regression analysis and the point estimates are pulled toward zero (Fig. 1).

Two principal components (PC) met the criteria of the Kaiser method (48). The results indicate an elevated OR with increased exposure as defined by PC 2, although not statistically significant (OR: 1.25, 95% CI: 0.94–1.66; $P = 0.13$; Table 5). The factor loadings in Table 5 indicate that PC 2 represents a mixture component that is positively weighted on BB-153 and BDE-153 and negatively weighted on BDE-209, suggesting that exposure to higher levels of BB-153 and/or BDE-153 while being less exposed to BDE-209 may have an adverse impact on cancer risk. Stratification by tumor size did not yield any statistically significant associations for any of the multi-pollutant methods.

Discussion

The results from this case–control study do not provide evidence of an increased risk of thyroid cancer in relation to PBDE exposure. Furthermore, some evidence of inverse associations is reported. This work, representing the largest epidemiologic study population to date and reporting on the greatest number of PBDE congeners, is consistent with the null results from the only two published studies on this topic that used serum biomarkers for the exposure assessment. However, the inverse findings for BDE-209 contrast with a positive association between house dust BDE-209 concentrations and PTC and reported by Hoffmann and colleagues (2017; ref. 37). We do report the first epidemiologic evidence

Table 3. Associations between PBDE serum concentrations and risk of PTC in 250 cases and 250 controls

PBDE Congener (ng/g)[a]	Controls	Cases	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)
BDE-28				
≤0.51	125	147	1	1
>0.51–≤1.65	100	78	0.66 (0.45–0.97)	0.67 (0.45–1.00)
>1.65	25	25	0.85 (0.47–1.56)	0.87 (0.46–1.65)
Continuous	250	250	0.96 (0.81–1.15)	0.94 (0.78–1.13)
BDE-47				
≤7.28	125	139	1	1
>7.28–≤24.91	100	90	0.81 (0.56–1.18)	0.80 (0.54–1.18)
>24.91	25	21	0.76 (0.40–1.42)	0.66 (0.34–1.28)
Continuous	250	250	0.91 (0.74–1.18)	0.89 (0.72–1.10)
BDE-85				
<LOD	161	176	1	1
≥LOD	89	74	0.76 (0.52–1.11)	0.71 (0.48–1.05)
Continuous[c]	—	—	—	—
BDE-99				
≤1.21	125	138	1	1
>1.21–≤5.00	100	94	0.85 (0.59–1.23)	0.83 (0.56–1.21)
>5.00	25	18	0.65 (0.34–1.25)	0.57 (0.29–1.12)
Continuous	250	250	0.93 (0.76–1.14)	0.91 (0.74–1.12)
BDE-100				
≤1.47	125	138	1	1
>1.47–≤5.43	100	91	0.82 (0.57–1.20)	0.78 (0.53–1.15)
>5.43	25	21	0.76 (0.41–1.43)	0.73 (0.38–1.41)
Continuous	250	250	1.07 (0.89–1.29)	1.05 (0.87–1.26)
BDE-153				
≤3.08	125	130	1	1
>3.08–≤14.02	100	88	0.85 (0.58–1.23)	0.85 (0.58–1.26)
>14.02	25	32	1.23 (0.69–2.19)	1.19 (0.66–2.16)
Continuous	250	250	1.08 (0.90–1.29)	1.08 (0.90–1.30)
BDE-154				
<LOD	152	164	1	1
≥LOD	98	86	0.81 (0.57–1.17)	0.78 (0.53–1.13)
Continuous[c]	—	—	—	—
BDE-183				
<LOD	176	185	1	1
≥LOD	74	65	0.84 (0.57–1.24)	0.74 (0.49–1.12)
Continuous[c]	—	—	—	—
BDE-209				
≤1.55	125	136	1	1
>1.55–≤4.08	100	100	0.92 (0.64–1.33)	0.90 (0.61–1.32)
>4.08	25	14	0.52 (0.26–1.03)	**0.47 (0.23–0.98)**
Continuous	250	250	0.90 (0.75–1.09)	0.87 (0.71–1.06)
BB-153				
≤1.45	125	129	1	1
>1.45–≤3.51	100	89	0.86 (0.59–1.26)	1.16 (0.76–1.76)
>3.51	25	32	1.24 (0.70–2.21)	1.81 (0.96–3.39)
Continuous	250	250	1.05 (0.87–1.27)	1.15 (0.88–1.52)

NOTE: Bold text indicates statistical significance ($P < 0.05$).
Abbreviation: LOD, limit of detection.
[a]Categories established on the basis of distributions among controls and correspond to either (i) ≤median, >median and ≤90th percentile, and >90th percentile for congeners with detection frequency ≥80% or (ii) undetected versus detected samples for congeners with detection frequency <80%.
[b]Adjusted for age, alcohol consumption, and years of education.
[c]Continuous models not run when detection frequency was <80%.

suggesting a positive association between BB-153 exposure and PTC risk.

Detection frequencies were higher for many congeners in our study samples compared with other studies (Supplementary Table S3), because our relatively large quantity of serum available for measurement (median: 2.00 g; 1st–99th percentile: 0.96–2.01 g) resulted in lower analytic detection limits. However, the median and 75th percentiles of serum BDE exposures in our

Table 4. Associations between PBDE serum concentrations and PTC risk stratified by tumor size

PBDE Congener (ng/g)[a]	Microcarcinomas < 1 cm (n = 138 cases)			Tumor size ≥ 1 cm (n = 110 cases)		
	Controls	Cases	Adjusted OR[b] (95% CI)	Controls	Cases	Adjusted OR[b] (95% CI)
BDE-28						
≤0.51	125	90	1	125	57	1
>0.51 to ≤1.65	100	33	0.43 (0.26–0.70)	100	43	1.00 (0.61–1.65)
>1.65	25	15	0.74 (0.36–1.55)	25	10	0.94 (0.40–2.19)
Continuous	250	138	0.84 (0.65–1.09)	250	110	1.00 (0.80–1.25)
BDE-47						
≤7.28	125	85	1	125	54	1
>7.28 to ≤24.91	100	41	0.57 (0.35–0.91)	100	47	1.09 (0.66–1.78)
>24.91	25	12	0.56 (0.25–1.22)	25	9	0.73 (0.31–1.74)
Continuous	250	138	0.85 (0.64–1.14)	250	110	0.91 (0.68–1.22)
BDE-85						
<LOD	161	107	1	161	68	1
≥LOD	89	31	**0.46 (0.28–0.76)**	89	42	1.08 (0.66–1.75)
Continuous[c]	—	—	—	—	—	—
BDE-99						
≤1.21	125	84	1	125	53	1
>1.21 to ≤5.00	100	44	0.59 (0.37–0.95)	100	49	1.09 (0.67–1.78)
>5.00	25	10	0.48 (0.21–1.10)	25	8	0.69 (0.28–1.69)
Continuous	250	138	0.94 (0.75–1.16)	250	110	0.77 (0.41–1.47)
BDE-100						
≤1.47	125	86	1	125	52	1
>1.47 to ≤5.43	100	43	**0.54 (0.34–0.86)**	100	46	1.09 (0.67–1.80)
>5.43	25	9	0.48 (0.21–1.10)	25	12	1.14 (0.52–2.51)
Continuous	250	138	1.04 (0.85–1.27)	250	110	1.06 (0.81–1.39)
BDE-153						
≤3.08	125	77	1	125	52	1
>3.08 to ≤14.02	100	45	0.72 (0.45–1.14)	100	42	1.01 (0.61–1.68)
>14.02	25	16	1.06 (0.52–2.16)	25	16	1.31 (0.63–2.74)
Continuous	250	138	1.06 (0.86–1.30)	250	110	1.11 (0.88–1.39)
BDE-154						
<LOD	152	98	1	152	65	1
≥LOD	98	40	**0.57 (0.36–0.91)**	98	45	1.02 (0.63–1.64)
Continuous[c]	—	—	—	—	—	—
BDE-183						
<LOD	176	109	1	176	74	1
≥LOD	74	29	**0.55 (0.33–0.93)**	74	36	1.05 (0.63–1.74)
Continuous[c]	—	—	—	—	—	—
BDE-209						
≤1.55	125	77	1	125	58	1
>1.55 to ≤4.08	100	54	0.85 (0.54–1.33)	100	45	0.94 (0.58–1.54)
>4.08	25	7	**0.40 (0.16–0.99)**	25	7	0.52 (0.20–1.34)
Continuous	250	138	0.75 (0.55–1.03)	250	110	0.94 (0.75–1.18)
BB-153						
≤1.45	125	66	1	125	63	1
>1.45 to ≤3.51	100	53	1.14 (0.70–1.85)	100	35	0.95 (0.55–1.63)
>3.51	25	19	1.60 (0.79–3.25)	25	12	1.46 (0.65–3.29)
Continuous	250	138	1.00 (0.63–1.58)	250	110	1.19 (0.89–1.59)

NOTE: Bold text indicates statistical significance ($P < 0.05$).

Abbreviation: LOD, limit of detection.

[a]Categories established on the basis of distributions among controls and correspond to either (i) ≤median, >median and ≤90th percentile, and >90th percentile for congeners with detection frequency ≥80% or (ii) undetected versus detected samples for congeners with detection frequency <80%.

[b]Adjusted for age, alcohol consumption, and years of education.

[c]Continuous models not run when detection frequency was <80%.

population tended to be lower compared with these other populations (Supplementary Table S3). The relatively low levels and limited contrast of exposures within our study population may have impeded our analyses and contributed to the generally null results. Further inquiry into explanations for the lower exposures in this population of Connecticut women as compared with a nationally representative sample or women living in other states could provide some valuable insights into exposure determinants or exposure mitigation.

The inconsistent relationships with thyroid cancer risk with respect to BDE-209 in serum in our study compared with those in

dust reported in Hoffman and colleagues (2017) could reflect differences in geographic region (Connecticut vs. North Carolina), the study population (women only with mean age of 51 years vs. men and women with mean age of 45 years), sample size (250 vs. 70 cases), or the exposure assessment methods (serum biomarker vs. dust; ref. 37). The two exposure assessment methods reflect different sources and exposure scenarios. PBDE biomarkers are a direct measure of dose which aggregate exposure across all pathways and routes PBDE concentrations in indoor dust are a useful surrogate for personal exposure within the home, and house dust is considered the major exposure source in U.S.
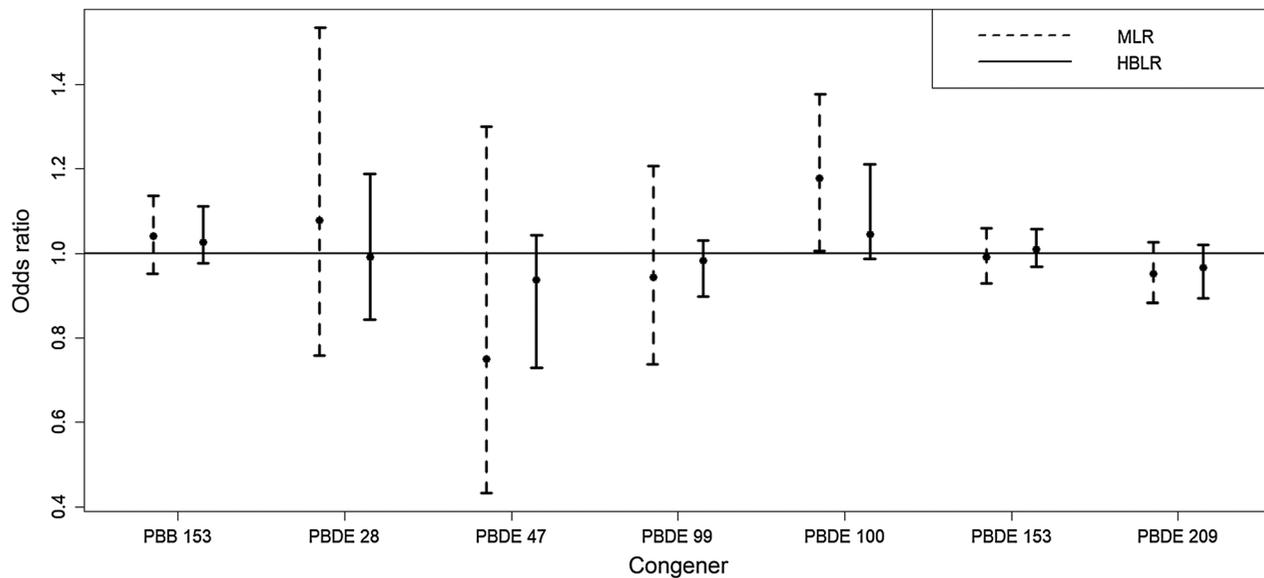
Figure 1.
Parameter estimates and 95% confidence/credible interval results from the standard multiple logistic regression (MLR) analysis and the hierarchical Bayesian multiple logistic regression (HBLR) analysis. Posterior means and quantile-based credible intervals are displayed for HBLR. The ORs represent the increase in odds for an interquartile range increase in exposure.

populations (13). House dust PBDE concentrations are also correlated with other measures of exposure, such as handwipes or biomonitoring (21, 49). However, dust levels do not capture exposures in other microenvironments, such as vehicles or workplaces, and they omit the dietary exposure pathway. The conflicting results with respect to BDE-209 may also reflect its different behaviors compared with other PBDEs. Most PBDE are readily absorbed internally and have long half-lives (on the order of years), and therefore serum PBDE concentrations are a reasonable proxy for longer-term exposures (Table 2; refs. 50, 51). In contrast, BDE-209, the fully brominated, larger, bulky molecule, has limited absorptive capacity and a short half-life. House dust concentrations of PBDE are correlated over time (52, 53), indicating that they provide a reasonable representation of past exposures; however, BDE-209 has been shown to photodegrade and debrominate into other congeners in house dust (54). Therefore, these two exposure assessment methods may be capturing different exposure time windows or may be reflecting some differences

related to the kinetics and chemistry of BDE-209. Additional studies measuring BDE-209 in both serum and dust are needed to clarify its relationship with thyroid cancer risk.

We conducted some multi-pollutant modeling to reflect more realistic exposure scenarios, as these congeners coexist in mixtures and may exhibit synergistic, antagonistic, or other interactions (55). The multi-pollutant models were generally consistent with the single-pollutant models. Both the PCA analysis and the single-pollutant model provided evidence for an inverse association with BDE-209 and a positive association between BB-153 exposure and PTC risk. An association between BDE-100 and PTC risk was only observed in the standard multi-pollutant regression model. Though use of BB-153 was discontinued in 1976, our finding is relevant, as people continue to be exposed to BB-153, and in combination with other thyroid hormone–disrupting chemicals (56, 57). Therefore, these results suggest some relationships to explore in future analyses. More advanced approaches to mixtures, such as a Bayesian statistical approach using toxicology data or kernel regression could reveal some new insights.

Several inverse associations between PBDE congeners and PTC microcarcinoma were observed in single-pollutant models but not in the multi-pollutant models. While chance findings cannot be ruled out, equivocal or inverted associations between structurally similar endocrine-disrupting compounds and hormone-related cancers have been observed before, such as with serum concentrations of PCBs and breast cancer (58, 59); effect estimates less than 1 are consistent with the thyroid cancer study using prediagnosis serum PBDE concentrations to assign exposure. Finally, a relatively small proportion of microcarcinoma are considered clinically significant, and therefore information on stage could bring more precision to this outcome.

These results should be interpreted in the context of some important limitations. A single sample was used to represent exposure during the relevant window of susceptibility. One-time

Table 5. Principal component (PC) analysis factor loadings and regression results

Compound	PC 1	PC 2
BB-153		0.933
BDE-28	0.432	
BDE-47	0.478	
BDE-99	0.461	
BDE-100	0.471	
BDE-153	0.387	0.205
BDE-209		−0.273
	OR (95% CI)[a]	
	0.98 (0.09–1.08)	1.25 (0.94–1.66)
	$P = 0.72$	$P = 0.13$

NOTE: Only factor loadings larger than 0.10 in absolute value are displayed for ease of interpretability.
[a]Adjusted for age, alcohol consumption, and years of education.

serum measurements of persistent pollutants are generally considered to be a reasonable proxies for past exposures due to the long biological half-lives of most of these congeners (i.e., 1–12 years; Table 2; ref. 51) and the correlation in repeated measures of structurally similar compounds measured within the same women over time (60, 61). However, there are possible variations over time due to changes in exposures, weight loss, and dietary changes (61). The assumption of representativeness of BDE-209 is less robust, given the relatively short half-life in the blood. Another limitation is that the blood sample was collected post-diagnosis. Although biomarker concentrations in retrospective studies could be subject to bias if influenced by the disease state, we consider thyroid cancer unlikely to modify serum PBDE or lipid concentrations if the individual was maintained on thyroid hormones, because the treatment is relatively specific to the thyroid gland (i.e., surgical removal and radioactive iodine treatment). In addition, the few positive/elevated relationships observed could have been due to chance or multiple comparisons. Another limitation is that the results may only be generalizable to Caucasian females. We also did not have information on tumor stage, which could indicate the aggressiveness of the tumor, and we lacked data on genetics, which could be important in relation to genetic polymorphisms that influence activity of enzymes that metabolize endogenous hormones or detoxify PBDEs (10).

In summary, this study overcame some methodologic limitations of prior studies by having a larger population, higher detection frequencies across a range of congeners including BDE-209, and accounting for mixtures. Limitations included a single post-diagnostic serum sample to assess exposure and a population with relatively low PBDE exposure. While some inverse associations were observed in single-pollutant models, a few positive associations were also observed in single- and multi-pollutant models. Overall, there is limited evidence to date in support of a positive relationship between PBDE exposure and thyroid cancer risk. However, there is also insufficient evidence to conclude no risk from PBDE, and therefore these relationships warrant follow-up, given the biological plausibility derived from their chemical structures, toxicologic evidence in human hormone studies, *in vitro* assays, and animal experiments, and a previously reported positive association for BDE-209 in dust. A prospective study with application of more advanced statistical approaches to analyze mixtures, incorporation of genetic polymorphisms, a population with higher exposure levels and increased exposure variability, and collection of both dust and serum samples could reveal new insights.

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