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Original Contribution

Polybrominated Diphenyl Ethers, Polybrominated Biphenyls, and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study

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A nested case-control study was carried out using data from the US Department of Defense cohort between 2000 and 2013 to investigate the associations of papillary thyroid cancer (PTC) with serum concentrations of polybrominated diphenyl ethers and polybrominated biphenyls. This study included 742 histologically confirmed PTC cases (in 341 women and 401 men) and 742 matched controls with prediagnostic serum samples from the Department of Defense Serum Repository. Lipid-corrected serum concentrations of 8 congeners were measured. Multivariate conditional logistic regression analyses were performed for classical PTC and follicular variant of PTC, respectively. We also examined effect modification by sex. BDE-28, a polybrominated diphenyl ether congener, was associated with significantly increased risk of classical PTC (for the third tertile vs. below the limit of detection, odds ratio = 2.09, 95% confidence interval: 1.05, 4.15; *P* for trend = 0.02), adjusting for other congeners, body mass index, and branch of military service. This association was observed mainly for larger classical PTC (tumor size > 10 mm), with a significantly stronger association among women than men (*P* for interaction = 0.004). No consistent associations were observed for other congeners, including those at higher concentrations. This study found a significantly increased risk of classical PTC associated with increasing levels of BDE-28. The risk varied by sex and tumor size.

papillary thyroid cancer; PBBs; PBDEs; polybrominated biphenyls; polybrominated diphenyl ethers

Abbreviations: BDE, brominated diphenyl ether; BMI, body mass index; CI, confidence interval; ICD-O-3, *International Classification of Diseases for Oncology*, *Third Revision*; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PTC, papillary thyroid cancer.

Thyroid cancer is the most prevalent cancer of the endocrine system, and its incidence has been increasing faster than that of any other malignancy (1). In the United States, the incidence of thyroid cancer increased by 148% among men (from 3.1 to 7.7 per 100,000 persons) and by 247% among women (from 6.4 to 22.2 per 100,000 persons) between 1975 and 2014 (2). A pattern of increasing rates was also observed in US military personnel, among men (from 2.53 to 2.76 per 100,000 persons) and women (from 9.62 to 13.51 per 100,000 persons) between the periods 1990–1997 and 1998–2004, and the incidence was significantly higher in military women than women in the general population for ages 20–49 years (3). The majority of the increase is for papillary thyroid cancer (PTC), the most common histological type, accounting for more than 80% of all thyroid carcinomas (4, 5). While the increased detection of occult disease has contributed to the increasing trend, it has also been suggested that environmental chemicals or physical agents play a role (6–8).

Since the 1970s, polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs) have been widely used as flame retardants among the US general and military population in a variety of commercial and household products, including plastics, furniture, upholstery, textiles,

electrical equipment, and electronic devices (9, 10). Because PBDEs and PBBs are physically mixed into products, they have the potential to release into the environment and enter the human body (9, 10). Environmental and human levels of PBDEs have been increasing rapidly in the last three decades (7). Due to concerns about increasing exposure and potential associations with adverse health outcomes, the US government banned the production of PBBs in 1976 and increased regulations on PBDEs in 2004 (11, 12). Despite this, PBDEs and PBBs remain ubiquitous in the environment and are being detected in human populations due to their persistence and bioaccumulation (7, 10). Among Michigan women exposed to PBBs in an accidental contamination of food supply (1973–1974), blood concentrations of PBB-153 in 2004 were still substantially higher when compared with National Health and Nutrition Examination Survey (NHANES) data 2003–2004 (13, 14). Although some investigations on temporal trends of PBDE body burdens suggest a moderate decline starting approximately after 2000 (12, 15), others have reported a significant increase of several PBDE congeners from 2011–2015 (11, 16). The observed trends suggest PBDEs could be following the trend of other legacy pollutants, where temporal declines were followed by an exposure plateau that persisted for decades (11, 15).

Experimental evidence has suggested that exposures to PBDEs and PBBs are related to disruption of thyroid hormone homeostasis and thyroid function in vitro and in rats (17, 18), but epidemiologic studies have yielded conflicting findings in the associations between PBDE and PBB exposures and thyroid function (13, 19–21).

Animal studies of carcinogenicity of PBDEs are limited to decabrominated diphenyl ethers (BDEs). These studies report a slightly elevated incidence of thyroid gland adenoma or carcinoma (combined) and a significantly increased incidence of follicular cell hyperplasia, which is considered to be a precursor of thyroid tumors, in exposed mice (9). To our knowledge, only two epidemiologic studies have investigated the relationship between exposure to PBDEs and risk of thyroid cancer. One study, including 70 PTC cases and 70 controls, reported a positive association with BDE-209 (22), while another, including 104 cases and 207 controls, did not find any associations (23). To our knowledge, no previous studies have evaluated PBB exposures in relation to risk of thyroid cancer.

Considering parallel increasing trends of thyroid cancer incidence and PBDE body burdens, combined with the paucity of epidemiologic studies directly investigating their association, we conducted a nested case-control study using data from the Department of Defense Automated Central Tumor Registry and the Defense Medical Surveillance System, with prediagnostic serum samples from the Department of Defense Serum Repository, to investigate the associations of PTC with serum concentrations of PBDEs and PBBs.

METHODS

Study population

Detailed information regarding the study design has been published elsewhere (24). In brief, 742 pairs of PTC cases and controls were selected from US military personnel who had serum samples stored in the Department of Defense Serum Repository. Serum samples from all military members were drawn during active duty. Inclusion criteria for cases: 1) histologically confirmed (*International Classification of Diseases for Oncology*, *Third Revision* (ICD-O-3): 8050, 8260, and 8340–8343); 2) at least 3 0.5-mL prediagnostic (total 1.5 mL) and 1 0.5-mL postdiagnostic serum samples stored in the Department of Defense Serum Repository since 1989; 3) diagnosis between 2000 and 2013; 4) age 21 years or older at diagnosis; and 5) without any cancers (except for nonmelanoma skin cancer) prior to the date of PTC diagnosis. Controls who had no diagnosis with any cancer (except for nonmelanoma skin cancer) were randomly selected and individually matched to cases on date of birth (within 1 year), sex, race/ethnicity, and midpoint of dates of the selected 4 samples drawn (within 1 year). Demographic and military characteristics for all participants were abstracted from the Defense Medical Surveillance System. All study procedures were approved by the Uniformed Services University Institutional Review Board, the Walter Reed National Military Medical Center, the Department of Defense Joint Pathology Center, and the Human Investigation Committee of Yale University. The involvement of the Centers for Disease Control and Prevention laboratory did not constitute engagement in human subjects research.

Measurement of PBDEs and PBBs

Serum concentrations of PBDEs and PBBs were measured in the earliest prediagnostic serum sample. The measurement was conducted at the Persistent Organic Pollutants Laboratory, Centers for Disease Control and Prevention (Atlanta, Georgia). The methodology used has been published (25). Briefly, the serum samples were at first automatically fortified with internal standards using Gilson 215 liquid handler (Gilson, Inc., Middleton, Wisconsin). The samples were then extracted by automated liquid-liquid extraction using a liquid handler. Removal of coextracted lipids was performed on a silica:silica/sulfuric acid column using the RapidTrace (Biotage; Uppsala, Sweden) equipment for automation. The final analytical determinations of PBDE and PBB congeners were performed by using gas chromatography, isotope dilution, high-resolution mass spectrometry employing a DFS (Thermo Fisher Scientific, Waltham, Massachusetts) instrument.

Laboratory personnel were blinded to case and control status. Internal laboratory controls included method blanks ($n = 3$) and duplicates ($n = 3$) in every set of 24 study samples. Serum concentrations of PBDE and PBB congeners were reported as the concentration after subtraction of the median amount of the congener present as a contaminant in blank samples.

A total of 11 PBDE congeners and 1 PBB congener were measured (Table 1). The detection rates for each PBDE and PBB congener were similar among cases and controls (P values from the χ^2 tests range: 0.089–0.90). Levels of the 12 congeners were reported as lipid-corrected serum concentration (ng/g of serum lipid). The distributions of the concentrations were similar between cases and controls

Table 1. Lipid-Corrected Serum Concentrations of Polybrominated Diphenyl Ether and Polybrominated Biphenyl Congeners (ng/g) Among Cases of Papillary Thyroid Cancer and Controls in the Department of Defense Cohort, United States, 2000–2013

Congener	Median LOD[a]	Cases				Controls				*P* Value[b]
		Detected[c]		GM (GSD)	Median (IQR)	Detected[c]		GM (GSD)	Median (IQR)	
		No.	%			No.	%			
BDE-17	1.0	41	5.5	2.1 (2.0)	–[d]	30	4.0	1.9 (1.9)	–[d]	0.18
BDE-28	1.1	251	33.8	3.0 (2.5)	<LOD (<LOD–1.5)	236	31.8	2.6 (2.3)	<LOD (<LOD–1.3)	0.25
BDE-47	2.5	708	95.4	21.5 (3.7)	16.3 (7.9–38.8)	707	95.3	21.0 (3.2)	16.9 (8.4–38.6)	0.74
BDE-66	1.2	66	8.9	2.9 (2.3)	–[d]	52	7.0	2.3 (2.1)	–[d]	0.15
BDE-85	1.0	208	28.0	3.3 (3.0)	<LOD (<LOD–1.0)	204	27.5	2.8 (2.6)	<LOD (<LOD–1.0)	0.67
BDE-99	2.0	549	74.0	9.1 (3.6)	4.3 (<LOD–10.6)	577	77.8	8.2 (3.2)	4.4 (2.2–10.6)	0.60
BDE-100	1.0	621	83.7	5.7 (3.5)	3.4 (1.5–8.8)	643	86.7	5.4 (3.0)	3.7 (1.8–8.7)	0.43
BDE-153	1.0	679	91.5	6.4 (3.4)	4.3 (2.1–11.5)	691	93.1	6.3 (3.0)	4.6 (2.5–11.2)	0.37
BDE-154	1.0	217	29.3	3.0 (2.9)	<LOD (<LOD–1.1)	209	28.2	2.6 (2.5)	<LOD (<LOD–1.0)	0.56
BDE-183	1.1	79	10.7	1.7 (2.0)	–[d]	85	11.5	1.5 (1.7)	–[d]	0.68
BDE-209	5.2	62	8.4	9.7 (2.2)	–[d]	80	10.8	8.5 (1.8)	–[d]	0.14
BB-153	1.0	544	73.3	3.0 (2.3)	2.0 (<LOD–3.5)	550	74.1	3.1 (2.2)	2.1 (0.9–3.6)	0.36

Abbreviations: BB-153, 2,2′,4,4′,5,5′-hexabromobiphenyl; BDE-17, 2,2′,4-tribromodiphenyl ether; BDE-28, 2,4,4′-tribromodiphenyl ether; BDE-47, 2,2′,4,4′-tetrabromodiphenyl ether; BDE-66, 2,3′,4′,4-tetrabromodiphenyl ether; BDE-85, 2,2′,3,4,4′-pentabromodiphenyl ether; BDE-99, 2,2′,4,4′,5-pentabromodiphenyl ether; BDE-100, 2,2′,4,4′,6-pentabromodiphenyl ether; BDE-153, 2,2′,4,4′,5,5′-hexabromodiphenyl ether; BDE-154, 2,2′,4,4′,5,6′-hexabromodiphenyl ether; BDE-183, 2,2′,3,4,4′,5′,6-heptabromodiphenyl ether; BDE-209, 2,2′,3,3′,4,4′,5,5′,6,6′-decabromodiphenyl ether; GM, geometric mean; GSD, geometric standard deviation; IQR, interquartile range; LOD: limit of detection.

[a] Calculated among cases and controls combined.

[b] Estimated by the Mann-Whitney *U* test.

[c] Cases or controls whose serum samples containing PBDE or PBB congener had an amount above the limit of detection, and the value of concentration is detectable.

[d] All values were below the limit of detection.

(*P* values from the Mann-Whitney *U* tests range: 0.14–0.74). We also examined the distributions of concentrations according to participants' demographic characteristics and military services; the results are summarized in Web Tables 1 and 2.

Statistical analyses

The distributions of demographic and military characteristics were compared between cases and controls using the χ^2 test. Because the distributions of lipid-corrected serum concentrations of PBDE and PBB congeners were right skewed, they were compared between cases and controls using the Mann-Whitney *U* test.

Among the 12 congeners measured, 7 PBDE congeners (BDE-28, -47, -85, -99, -100, -153, and -154) and the PBB congener (BB-153) that were detected in >20% of the control samples were included in the final analyses. For the 5 congeners with ≤25% of data below the limits of detection (LODs) (BDE-47, -99, -100, and -153, and BB-153), the lipid-corrected serum concentrations were categorized into quartiles based on the distribution among controls, with the first quartile used as the reference category. For congeners with >25% of data below the LODs (BDE-28, -85, and -154), the reference values were defined as those below the LODs, and the values above the LODs were categorized into tertiles.

Given the individual-matched case-control design, conditional logistic regression models were used to estimate the associations between risk of PTC and levels of PBDE and PBB congeners. We applied two approaches: single-chemical models and multichemical models. Both single- and multichemical models adjusted for body mass index (BMI) and branch of military service. Additional adjustment for the years between serum sample collection and PTC diagnosis did not change the results, so this variable was not included in the final models. In the single-chemical models, the associations between risk of PTC and concentrations of each PBDE congener and the PBB-153 were individually estimated. In the multichemical model, we included all the categorical PBDE and PBB congeners in one model to additionally control for potential confounding from other congeners. Given that the categorized congeners were not highly correlated (Cramer's *V* range: 0.05–0.73; Web Table 3), the estimated associations are not likely to be affected by multicollinearity.

Statistical analyses were performed for histological subtype, classical PTC (ICD-O-3: 8050, 8260, 8341–8343), and

Table 2. Distributions of Selected Characteristics Among Cases of Papillary Thyroid Cancer and Controls in the Department of Defense Cohort, United States, 2000–2013

Characteristic	Cases		Controls		*P* Value[a]
	No.	%	No.	%	
Age at serum sample collection, years					
<20	124	16.7	121	16.3	
20–29	348	46.9	352	47.4	
30–40	220	29.7	221	29.8	
≥40	50	6.7	48	6.5	0.99
Age at diagnosis, years					
<30	210	28.3	203	27.4	
30–39	310	41.8	323	43.5	
40–49	185	24.9	179	24.1	
≥50	37	5.0	37	5.0	0.92
Sex					
Male	401	54.0	401	54.0	
Female	341	46.0	341	46.0	1.00
Ethnicity					
White	468	63.1	467	63.0	
Black	131	17.7	132	17.8	
Hispanic	68	9.2	68	9.2	
Other	55	7.4	55	7.4	
Unknown	20	2.7	20	2.7	1.00
BMI[b]					
<25.0	257	34.6	285	38.4	
25.0–29.9	148	20.0	129	17.4	
≥30.0	16	2.2	10	1.4	
Missing	321	43.3	318	42.9	0.25
Service					
Army	300	40.4	263	35.4	
Air Force	197	26.6	152	20.5	
Marines and Coast Guard, combined	61	8.2	83	11.2	
Navy	184	24.8	244	32.9	0.0002
Year of serum sample collection					
1994–2000	570	76.8	571	77.0	
2001–2004	135	18.2	133	17.9	
2005–2009	37	5.0	38	5.1	0.99
Years between serum sample collection and PTC diagnosis					
<5	115	15.5			
5–9	344	46.4			
10–12	283	38.1			
Histological subtype					
Classical PTC	600	80.9			
Follicular variant of PTC	142	19.1			

Table continues

Table 2. Continued

Characteristic	Cases		Controls		*P* Value[a]
	No.	%	No.	%	
Tumor size, mm					
≤10	235	31.7			
>10	463	62.4			
Missing	44	5.9			

Abbreviations: BMI, body mass index; PTC, papillary thyroid cancer.
[a] Estimated by the χ^2 test.
[b] Weight (kg)/height (m)^2.

follicular variant of PTC (ICD-O-3: 8340), respectively. Further stratified analyses were conducted according to tumor size (classical PTC microcarcinoma with tumor size ≤10 mm and large classical PTC with tumor size >10 mm) and then according to sex among classical PTC cases and matched controls, but not for follicular variant of PTC due to small case numbers. Dose-response relationships were investigated using tests for trend by assigning each participant the quartile number of PBDE and PBB congeners. A sensitivity analysis was conducted by excluding participants whose serum samples were drawn within a likely latency period (<5 years before diagnosis) among classical PTC cases and matched controls (26). The remaining participants were stratified by tumor size and each cutpoint of years between the time of serum sample collection and PTC diagnosis (5–12 years) to evaluate whether the timing of sample collection modified the associations.

All tests were 2-sided with $\alpha = 0.05$. Because 7 PBDE and 1 PBB congeners were included in the final analysis, a Bonferroni-adjusted α of $0.05/8 = 0.006$ was applied to control for multiple comparisons. Because single- and multichemical models provided similar risk estimates, all results are presented from the multichemical models. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc.; Cary, North Carolina).

RESULTS

As shown in Table 2, PTC cases were more likely to have served in the Army or Air Force at the time of diagnosis, whereas controls were more likely to have served in the Navy or Marines/Coast Guard. Because of matching criteria, distributions of age, sex, race/ethnicity, and date of sample drawn were similar between cases and controls. Distribution of BMI was also similar between cases and controls, although there was a high percentage of participants with missing BMI data.

All serum samples used for the measurement of PBDEs and PBBs were drawn during 1994–2009 and 1,132–4,383 days (approximately 3–12 years) before the cases were diagnosed with PTC. The median age at sample collection was 25 years (interquartile range, 21–32 years).

An elevated risk of classical PTC was associated with higher levels of BDE-28 (for the third tertile vs. below LOD, odds ratio (OR) = 2.09, 95% confidence interval (CI): 1.05, 4.15; *P* for trend = 0.020) (Table 3), although the *P* for trend was no longer significant after the Bonferroni adjustment. A borderline significantly reduced odds ratio was observed for the second tertile of BDE-85 (OR = 0.43, 95% CI: 0.19, 0.99). There were no associations between individual PBDE congeners or PBB-153 and risk of follicular variant of PTC.

When the analyses were further stratified by tumor size of classical PTC, an increased risk associated with higher levels of BDE-28 was observed only for large classical PTC (for the second tertile vs. below LOD, OR = 2.35, 95% CI: 1.15, 4.80; for the third tertile vs. below LOD, OR = 4.77, 95% CI: 1.84, 12.35; *P* for trend = 0.0014) (Table 4). The *P* for trend remained significant after the Bonferroni adjustment. There were significantly increased odds ratios for large classical PTC with BDE-154 for the first and second tertiles versus below LOD (OR = 3.33, 95% CI: 1.50, 7.36, and OR = 3.40, 95% CI: 1.18, 9.85, respectively) but not for the third tertile versus below LOD (*P* for trend = 0.039). For classical PTC microcarcinoma, there were significantly decreased odds ratios with BDE-154 for the second and third tertiles versus below LOD (OR = 0.15, 95% CI: 0.02, 0.93, and OR = 0.04, 95% CI: <0.01, 0.51, respectively; *P* for trend = 0.017). A significantly reduced odds ratio was also observed for large classical PTC with the second tertile of BDE-85 (OR = 0.23, 95% CI: 0.08, 0.65). No association was observed for the other PBDE and PBB congeners in relation to either large classical PTC or classical PTC microcarcinoma.

Sex significantly modified the associations between levels of BDE-28 and risk of large classical PTC (Table 5). The association between serum levels of BDE-28 and risk of large classical PTC was stronger in women (for the third tertile vs. below LOD, OR = 10.74, 95% CI: 1.93, 59.72; *P* for trend = 0.0054) than men (for the third tertile vs. below LOD, OR = 3.39, 95% CI: 0.98, 11.71; *P* for trend = 0.071 and *P* for interaction = 0.0040). After Bonferroni adjustment, the *P* for trend remained significant only among women, and the effect modification by sex remained significant. No significant association was observed for the other

Table 3. Risk of Papillary Thyroid Cancer Associated With Lipid-Corrected Serum Concentrations of Polybrominated Diphenyl Ether and Polybrominated Biphenyl Congeners (ng/g) Among Cases and Controls, Stratified by Histological Subtype, Department of Defense Cohort, United States, 2000–2013

Congener and Concentration	Classical PTC				Follicular Variant of PTC			
	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI
BDE-28								
<LOD	383	406	1.00	Referent	97	88	1.00	Referent
>LOD–1.56	55	63	0.91	0.57, 1.45	16	15	1.06	0.40, 2.80
1.57–3.18	68	62	1.58	0.93, 2.69	11	17	0.42	0.12, 1.40
3.19–80.10	87	61	2.09	1.05, 4.15	14	18	0.39	0.07, 2.23
P for trend[c]				0.020				0.35
BDE-47								
<LOD–8.43	159	150	1.00	Referent	36	32	1.00	Referent
8.44–16.91	141	150	1.16	0.74, 1.81	38	33	1.18	0.43, 3.26
16.92–38.63	137	142	1.37	0.74, 2.54	36	40	0.94	0.24, 3.58
38.64–2,189.00	156	150	1.00	0.41, 2.44	28	33	2.74	0.36, 20.64
P for trend[c]				0.89				0.95
BDE-85								
<LOD	423	433	1.00	Referent	102	99	1.00	Referent
>LOD–1.68	61	55	1.06	0.58, 1.95	15	12	1.49	0.41, 5.44
1.69–3.18	30	56	0.43	0.19, 0.99	6	13	1.18	0.21, 6.52
3.19–79.08	81	53	1.76	0.57, 5.47	15	15	4.98	0.31, 79.67
P for trend[c]				0.64				0.34
BDE-99								
<LOD–2.17	168	149	1.00	Referent	40	35	1.00	Referent
2.18–4.40	133	150	0.87	0.55, 1.35	29	34	0.93	0.37, 2.35
4.41–10.61	142	147	0.92	0.52, 1.62	39	37	1.88	0.53, 6.69
10.62–993.30	152	151	0.86	0.39, 1.87	30	33	1.65	0.32, 8.45
P for trend[c]				0.59				0.22
BDE-100								
<LOD–1.84	177	151	1.00	Referent	39	31	1.00	Referent
1.85–3.71	134	148	0.73	0.46, 1.18	36	35	0.53	0.19, 1.47
3.72–8.65	120	144	0.61	0.32, 1.17	39	38	0.33	0.07, 1.53
8.66–368.00	162	149	0.67	0.27, 1.65	24	34	0.19	0.03, 1.41
P for trend[c]				0.29				0.13
BDE-153								
<LOD–2.49	176	146	1.00	Referent	36	38	1.00	Referent
2.50–4.61	134	155	0.82	0.57, 1.18	38	29	1.91	0.84, 4.36
4.62–11.23	122	154	0.69	0.45, 1.08	39	30	2.08	0.81, 5.35
11.24–285.50	163	142	0.94	0.55, 1.61	25	42	0.78	0.24, 2.57
P for trend[c]				0.71				0.94

Table continues

Table 3. Continued

Congener and Concentration	Classical PTC				Follicular Variant of PTC			
	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI
BDE-154								
<LOD	412	426	1.00	Referent	102	95	1.00	Referent
>LOD–1.60	60	54	1.49	0.82, 2.70	16	15	0.97	0.29, 3.29
1.61–3.11	50	57	1.37	0.61, 3.07	6	13	0.39	0.07, 2.26
3.12–66.22	71	55	0.61	0.19, 1.99	14	15	0.85	0.06, 13.17
P for trend[c]				0.49				0.76
BB-153								
<LOD–0.85	154	149	1.00	Referent	1.00	33	1.00	Referent
0.86–2.12	146	146	0.91	0.65, 1.28	38	37	0.87	0.41, 1.84
2.13–3.60	152	155	0.85	0.60, 1.21	31	27	1.25	0.56, 2.79
3.61–451.30	141	142	0.92	0.65, 1.31	32	41	0.76	0.35, 1.68
P for trend[c]				0.47				0.60

Abbreviations: BB-153, 2,2′,4,4′,5,5′-hexabromobiphenyl; BDE-28, 2,4,4′-tribromodiphenyl ether; BDE-47, 2,2′,4,4′-tetrabromodiphenyl ether; BDE-85, 2,2′,3,4,4′-pentabromodiphenyl ether; BDE-99, 2,2′,4,4′,5-pentabromodiphenyl ether; BDE-100, 2,2′,4,4′,6-pentabromodiphenyl ether; BDE-153, 2,2′,4,4′,5,5′-hexabromodiphenyl ether; BDE-154, 2,2′,4,4′,5,6′-hexabromodiphenyl ether; BMI, body mass index; CI, confidence interval; LOD: limit of detection; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PTC, papillary thyroid cancer.

[a] Values in subgroups do not sum to the total due to nonreportable values.

[b] Multichemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI (calculated as weight (kg)/height (m)^2: <18.5, 18.5–24.9, 25.0–29.9, ≥30.0, or missing), and branch of military service (Army, Air Force, Navy, and Marines/Coast Guard).

[c] *P* values were not corrected for multiple comparison.

PBDE and PBB congeners among either men or women. Null associations between levels of BDE-28 and risk of classical PTC microcarcinoma were found among both men and women (Web Table 4).

The association between BDE-28 and risk of classical PTC was stronger after exclusion of case-control pairs whose serum samples were drawn <5 years before cancer diagnosis (for the second tertile vs. below LOD, OR = 1.80, 95% CI: 1.00, 3.21; for the third tertile vs. below LOD, OR = 2.53, 95% CI: 1.19, 5.36; *P* for trend = 0.014) (Web Table 5). The associations for most other congeners were also slightly strengthened in this sensitivity analysis. Similar associations were observed for BDE-153 before and after exclusion samples drawn <5 years from diagnosis. There was no effect modification by timing of sample collection for either large classical PTC or classical PTC microcarcinoma (data not shown).

DISCUSSION

In this large, nested case-control study among US military personnel, we found that increasing serum levels of BDE-28 were associated with an elevated risk of classical PTC. This association was observed mainly for classical PTC among cases with tumor size >10 mm, and it was stronger among women.

The geometric means of concentration for BDE-28, -47, -99, -100, and -153 and BB-153 in controls of this study were higher than those in the US general population from the NHANES 2003–2004 (14). When we restricted our comparisons to the subset of our study population with serum samples taken during 2003–2004, the geometric means were comparable to those in the NHANES 2003–2004 population. However, the 90th and 95th percentiles of concentrations for most PBDE and PBB congeners in this study population were lower than those in the NHANES 2003–2004 population, indicating a more centralized range of concentrations in the present military population than among the NHANES general population. A similar range of concentrations was observed only for BDE-153 between the study population and NHANES 2003–2004 population.

Although accumulating evidence has illustrated that exposure to PBDEs and PBBs alters thyroid hormone homeostasis, the underlying mechanisms linking PBDEs and PBBs to thyroid cancer are not fully understood. Because the chemical structures of PBDE and PBB congeners are similar to those of thyroid hormones, the hydroxylated metabolites of PBDEs and PBBs could competitively bind to thyroid hormone transport proteins and receptors (7). Additionally, PBDEs can induce thyroid hormone metabolic enzyme activity (7). These two potential mechanisms suggest that PBDEs and PBBs could disrupt thyroid hormone homeostasis and could contribute to cancer risk and severity (22).

In a recent prospective cohort study (27), investigators reported that significant decrements in thyroid-stimulating

Table 4. Risk of Classical Papillary Thyroid Cancer Associated With Lipid-Corrected Serum Concentrations of Polybrominated Diphenyl Ether and Polybrominated Biphenyl Congeners (ng/g) Among Cases Controls, Stratified by Tumor Size, Department of Defense Cohort, United States, 2000–2013

Congener and Concentration	≤10 mm				>10 mm			
	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI
BDE-28								
<LOD	141	125	1.00	Referent	215	249	1.00	Referent
>LOD–1.56	14	22	0.47	0.19, 1.19	40	39	1.33	0.73, 2.42
1.57–3.18	22	22	0.82	0.30, 2.22	43	37	2.35	1.15, 4.80
3.19–80.10	25	30	0.55	0.16, 1.87	58	31	4.77	1.84, 12.35
P for trend[c]			0.57				0.0014	
BDE-47								
<LOD–8.43	62	48	1.00	Referent	89	91	1.00	Referent
8.44–16.91	44	47	0.99	0.43, 2.32	84	92	1.27	0.70, 2.30
16.92–38.63	44	50	1.23	0.41, 3.76	87	81	1.49	0.65, 3.46
38.64–2,189.00	52	54	2.86	0.48, 17.10	96	92	0.61	0.18, 2.10
P for trend[c]			0.54				0.75	
BDE-85								
<LOD	151	142	1.00	Referent	244	258	1.00	Referent
>LOD–1.68	19	22	2.68	0.81, 8.83	39	30	0.61	0.27, 1.38
1.69–3.18	7	14	3.93	0.52, 29.91	22	41	0.23	0.08, 0.65
3.19–79.08	25	24	13.41	0.97, 185.94	53	29	0.93	0.23, 3.83
P for trend[c]			0.017				0.067	
BDE-99								
<LOD–2.17	63	50	1.00	Referent	94	87	1.00	Referent
2.18–4.40	44	47	0.95	0.42, 2.15	82	92	0.83	0.46, 1.52
4.41–10.61	46	49	1.16	0.42, 3.19	86	88	0.74	0.34, 1.62
10.62–993.30	49	56	0.90	0.19, 4.34	96	91	0.68	0.24, 1.92
P for trend[c]			0.92				0.46	
BDE-100								
<LOD–1.84	69	49	1.00	Referent	97	86	1.00	Referent
1.85–3.71	43	48	0.57	0.25, 1.33	82	95	0.66	0.35, 1.25
3.72–8.65	43	49	0.51	0.16, 1.65	70	82	0.61	0.25, 1.48
8.66–368.00	47	53	0.26	0.05, 1.32	107	93	0.83	0.24, 2.82
P for trend[c]			0.094				0.72	
BDE-153								
<LOD–2.49	67	49	1.00	Referent	98	86	1.00	Referent
2.50–4.61	48	57	0.76	0.40, 1.44	76	86	0.94	0.58, 1.53
4.62–11.23	38	55	0.80	0.37, 1.76	81	87	0.84	0.47, 1.50
11.24–285.50	49	41	2.74	0.96, 7.86	103	99	0.66	0.33, 1.32
P for trend[c]			0.21				0.33	
BDE-154								
<LOD	155	135	1.00	Referent	230	258	1.00	Referent
>LOD–1.60	14	20	0.35	0.11, 1.14	44	31	3.33	1.50, 7.36
1.61–3.11	10	18	0.15	0.02, 0.93	37	38	3.40	1.18, 9.85
3.12–66.22	23	26	0.04	<0.01, 0.51	45	29	1.74	0.39, 7.80
P for trend[c]			0.017				0.039	

Table continues

Table 4. Continued

Congener and Concentration	≤10 mm				>10 mm			
	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI
BB-153								
<LOD–0.85	48	43	1.00	Referent	92	92	1.00	Referent
0.86–2.12	51	49	1.02	0.55, 1.90	88	84	0.81	0.51, 1.28
2.13–3.60	55	54	0.86	0.46, 1.62	90	95	0.74	0.47, 1.18
3.61–451.30	48	53	0.87	0.45, 1.67	86	85	0.85	0.54, 1.36
P for trend[c]			0.42				0.67	

Abbreviation: BB-153, 2,2′,4,4′,5,5′-hexabromobiphenyl; BDE-28, 2,4,4′-tribromodiphenyl ether; BDE-47, 2,2′,4,4′-tetrabromodiphenyl ether; BDE-85, 2,2′,3,4,4′-pentabromodiphenyl ether; BDE-99, 2,2′,4,4′,5-pentabromodiphenyl ether; BDE-100, 2,2′,4,4′,6-pentabromodiphenyl ether; BDE-153, 2,2′,4,4′,5,5′-hexabromodiphenyl ether; BDE-154, 2,2′,4,4′,5,6′-hexabromodiphenyl ether; BMI, body mass index; CI, confidence interval; LOD: limit of detection; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PTC, papillary thyroid cancer.

[a] Values in subgroups do not sum to the total due to nonreportable values.

[b] Multichemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI (calculated as weight (kg)/height (m)^2: <18.5, 18.5–24.9, 25.0–29.9, ≥30.0, or missing), and branch of military service (Army, Air Force, Navy, and Marines/Coast Guard).

[c] *P* values were not corrected for multiple comparison.

hormone levels of 3-year-olds were associated with increased prenatal serum concentrations of several PBDE congeners, including BDE-28. This inverse relationship was modified by child sex, with stronger decrease in thyroid-stimulating hormone among girls. Because there is an indication from two other prospective cohort studies (24, 28) that lower levels of thyroid-stimulating hormone are associated with a significantly increased risk of thyroid cancer, it is possible that elevated levels of BDE-28 increase the risk of classical PTC through the mediation of thyroid-stimulating hormone.

Although the latency period between chemical exposure and appearance of thyroid cancer is still unclear, a latency period of 5–10 years has been reported for thyroid cancer after radiation exposure (26). The present study included only samples collected ≥3 years before PTC diagnosis. We also observed a stronger association between BDE-28 and risk of classical PTC among cases whose serum samples were drawn ≥5 years before cancer diagnosis.

To our knowledge, only two epidemiologic studies have investigated the associations between PBDE congeners and risk of thyroid cancer. One hospital-based case-control study investigated PBDEs in house dust and serum samples of 70 PTC cases and 70 noncancer controls (22). An elevated risk of PTC associated with a higher dust level of BDE-209 was observed, but no association with serum concentrations of any PBDE congeners was reported. Another nested case-control study including 104 incident thyroid cancer cases and 207 matched controls in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort reported no association between PBDEs and risk of thyroid cancer. The main congener found to be associated with PTC risk in our study (i.e., BDE-28) had a low detection rate in both previous studies, and the risk of thyroid cancer was not evaluated.

BDE-28 mainly exists in the penta-BDE commercial mixture (11), which is commonly used as flame retardant in flexible polyurethane foam and is also used in printed circuit boards and other applications. A recent study reported a unique trend of BDE-28 body burdens, which was decreasing from 2008–2009 to 2011–2012, flattened between 2011–2012 and 2014, and then increasing in 2014, among pregnant women in California (11). This recently increasing trend of BDE-28 might be due to the debromination of the higher brominated congeners (11), but this possibility must still be further explored.

The present study has several strengths. The sample size was relatively large, providing sufficient statistical power to investigate and compare the associations by sex, which is important because women are approximately 3 times more likely to develop thyroid cancer than men. The study population was composed entirely of US active-duty military personnel, a younger population that represents the age groups at which thyroid cancer risk is at its highest. Additionally, the single-payer, universal (i.e., equal access) military health-care system minimizes potential selection bias from differences in access to medical care. Although we did not suspect a specific source of exposure to PBDEs related to military service, PBDEs are persistent, with half-life ranges of 3–12 years, and temporal trends of levels measured in the environment suggest that human exposure is widespread despite bans on the various BDEs. The levels of PBDE and PBB congeners were prospectively assessed in the Department of Defense Serum Repository cohort, which provides an opportunity to estimate potentially causal relationships between exposure to these chemicals and risk of thyroid cancer.

The limitations of this study should also be considered. There was a lack of information on several potential confounding factors, such as ionizing radiation exposure,

Table 5. Risk of Large Classical Papillary Thyroid Cancer (>10 mm) Associated With Lipid-Corrected Serum Concentrations of Polybrominated Diphenyl Ether and Polybrominated Biphenyl Congeners (ng/g) Among Cases and Controls, Stratified by Sex, Department of Defense Cohort, United States, 2000–2013

Congener and Concentration	Male				Female				*P* for Interaction[b]
	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI	
BDE-28									
<LOD	129	138	1.00	Referent	86	111	1.00	Referent	
>LOD–1.56	25	21	1.50	0.69, 3.26	15	18	1.13	0.39, 3.30	
1.57–3.18	26	25	2.07	0.86, 4.94	17	12	3.56	0.87, 14.63	
3.19–80.10	26	20	3.39	0.98, 11.71	32	11	10.74	1.93, 59.72	
P for trend[c]			0.071				0.0054		0.0040
BDE-47									
<LOD–8.43	52	50	1.00	Referent	37	41	1.00	Referent	
8.44–16.91	52	46	1.26	0.56, 2.82	32	46	1.43	0.57, 3.59	
16.92–38.63	56	54	0.94	0.31, 2.87	31	27	3.08	0.79, 12.02	
38.64–2,189.00	46	54	0.41	0.08, 2.12	50	38	0.67	0.07, 6.09	
P for trend[c]			0.47				0.70		0.0095
BDE-85									
<LOD	148	142	1.00	Referent	96	116	1.00	Referent	
>LOD–1.68	25	23	0.56	0.21, 1.45	14	7	1.03	0.17, 6.40	
1.69–3.18	11	21	0.28	0.08, 1.02	11	20	0.17	0.02, 1.49	
3.19–79.08	22	19	0.40	0.07, 2.52	31	10	2.46	0.12, 51.74	
P for trend[c]			0.065				0.50		0.0087
BDE-99									
<LOD–2.17	54	47	1.00	Referent	40	40	1.00	Referent	
2.18–4.40	51	50	0.89	0.39, 2.03	31	42	0.72	0.29, 1.81	
4.41–10.61	52	52	1.02	0.34, 3.02	34	36	0.48	0.14, 1.61	
10.62–993.30	49	56	1.00	0.24, 4.25	47	35	0.51	0.09, 2.85	
P for trend[c]			0.92				0.33		0.036
BDE-100									
<LOD–1.84	55	45	1.00	Referent	42	41	1.00	Referent	
1.85–3.71	49	48	0.74	0.31, 1.77	33	47	0.58	0.21, 1.56	
3.72–8.65	46	52	0.73	0.22, 2.35	24	30	0.43	0.10, 1.89	
8.66–368.00	56	59	0.89	0.18, 4.36	51	34	0.91	0.09, 9.18	
P for trend[c]			0.88				0.60		0.014
BDE-153									
<LOD–2.49	48	32	1.00	Referent	50	54	1.00	Referent	
2.50–4.61	45	49	0.78	0.40, 1.54	31	37	0.95	0.44, 2.07	
4.62–11.23	51	55	0.82	0.38, 1.76	30	32	0.70	0.25, 1.96	
11.24–285.50	62	69	0.59	0.23, 1.55	41	30	0.59	0.18, 1.91	
P for trend[c]			0.39				0.50		0.077

Table continues

Table 5. Continued

Congener and Concentration	Male				Female				*P* for Interaction[b]
	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI	No. of Cases[a]	No. of Controls[a]	OR[b]	95% CI	
BDE-154									
<LOD	139	141	1.00	Referent	91	117	1.00	Referent	
>LOD–1.60	28	22	2.57	0.98, 6.73	16	9	4.43	0.94, 20.80	
1.61–3.11	18	24	2.59	0.69, 9.64	19	14	4.65	0.56, 38.40	
3.12–66.22	21	17	3.45	0.52, 22.96	24	12	0.54	0.02, 13.54	
P for trend[c]			0.061				0.40		0.0070
BB-153									
<LOD–0.85	41	34	1.00	Referent	51	58	1.00	Referent	
0.86–2.12	41	41	0.66	0.32, 1.35	47	43	0.84	0.44, 1.63	
2.13–3.60	61	63	0.67	0.35, 1.27	29	32	0.83	0.40, 1.75	
3.61–451.30	63	66	0.70	0.37, 1.34	23	19	0.99	0.42, 2.32	
P for trend[c]			0.46				0.92		0.16

Abbreviations: BB-153, 2,2′,4,4′,5,5′-hexabromobiphenyl; BDE-28, 2,4,4′-tribromodiphenyl ether; BDE-47, 2,2′,4,4′-tetrabromodiphenyl ether; BDE-85, 2,2′,3,4,4′-pentabromodiphenyl ether; BDE-99, 2,2′,4,4′,5-pentabromodiphenyl ether; BDE-100, 2,2′,4,4′,6-pentabromodiphenyl ether; BDE-153, 2,2′,4,4′,5,5′-hexabromodiphenyl ether; BDE-154, 2,2′,4,4′,5,6′-hexabromodiphenyl ether; BMI, body mass index; CI, confidence interval; LOD: limit of detection; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether.

[a] Values in subgroups do not sum to the total due to nonreportable values.

[b] Multichemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI (calculated as weight (kg)/height $(m)^2$: <18.5, 18.5–24.9, 25.0–29.9, ≥30.0, or missing), and branch of military service (Army, Air Force, Navy, and Marines/Coast Guard).

[c] *P* values were not corrected for multiple comparison.

history of benign thyroid disease, and a family history of thyroid cancer. Also, a high percentage of participants were missing BMI data, which could have led to insufficient adjustment for BMI. Previous evidence has suggested lower prevalence of obesity and larger lean body mass among military personnel than the US civilian population (29), indicating less variation of BMI among the US military personnel. Thus, any residual confounding of BMI would likely be minimized in this study population. We also restricted the analysis among case-control pairs who had BMI measurements; the associations remained the same. Furthermore, the stratified analyses and the results for follicular variant of PTC could have yielded unstable results due to the small subgroup counts. It is also possible that the findings for BDE-28 were observed by chance due to multiple comparisons. However, the association between BDE-28 and large classical PTC remained statistically significant after Bonferroni adjustment, indicating a true association.

In conclusion, this large nested case-control study suggested a significantly increased risk of classical PTC associated with increasing levels of BDE-28. This increased risk was found for cases with a tumor size >10 mm, and particularly among women. Because a recent study reported an increasing trend of BDE-28 concentrations in the serum of pregnant women in California in 2008–2014 (11), and accumulated evidence has suggested potential adverse influence on the thyroid for PBDE alternatives (22, 30), further investigation into the association between BDE-28, other PBDE congeners and alternatives, and thyroid cancer is warranted. Additionally, more epidemiologic studies among different populations are also warranted to confirm these findings and identify high-risk populations who are susceptible to these chemicals.

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