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Original Contribution

Polybrominated Diphenyl Ethers and Thyroid Cancer Risk in the Prostate, Colorectal, Lung, and Ovarian Cancer Screening Trial Cohort

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Polybrominated diphenyl ethers (PBDEs) alter thyroid hormone homeostasis, but their relationship with thyroid cancer is unknown. To investigate whether serum concentrations of PBDE were associated with thyroid cancer, we conducted a nested, case-control study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a large multicenter clinical trial in the United States. Cases with thyroid cancer ($n = 104$) were recruited from 1992 to 2001 and diagnosed through 2009, and controls ($n = 208$) were individually matched (2:1) to cases by race, sex, birth date (within 1 year), center, and blood collection date (within 15 days). We used gas chromatography isotope dilution high-resolution mass spectrometry to measure 10 tri- to heptabrominated diphenyl eithers in serum samples. Odds ratios and 95% confidence intervals were calculated using conditional logistic regression for lipid-adjusted PBDE levels detected in more than 50% of controls and for the sum of these BDEs ($\sum$PBDEs). We observed no significant differences between cases and controls in lipid-adjusted concentrations of $\sum$PBDEs (for cases, median = 12.8 ng/g lipid (interquartile range, 6.2–42.1); for controls, median = 19.4 ng/g lipid (interquartile range, 7.6–50.2)) or for individual congeners. Increasing quartiles of $\sum$PBDEs and 4 BDE congeners were not associated with risk of thyroid cancer (for the fourth vs. first quartile of $\sum$PBDEs, adjusted odd ratio = 0.62, 95% confidence interval: 0.29, 1.30; P for trend = 0.56). Our study does not support an association between exposure to PBDEs and thyroid cancer.

brominated diphenyl ethers; flame retardants; thyroid cancer risk

Abbreviations: BDE, brominated diphenyl ether; BMI, body mass index; IQR, interquartile range; LOD, limits of detection; PBDE, polybrominated diphenyl ether; PLCO, Prostate, Lung, Colorectal, and Ovarian.

Over the period of 1975–2009, the incidence of thyroid cancer increased 122% among men (from 3.1 to 6.9 per 100,000 persons) and 229% among women (from 6.5 to 21.4 per 100,000 persons) in the United States (1, 2), and increases of a similar magnitude occurred in other industrialized countries (3). The rapid increase and the international variation in thyroid cancer rates might partly reflect differences in exposure to environmental risk factors (3). Since the 1970s, polybrominated diphenyl ethers (PBDEs) have been widely used as flame retardants in the United States in a variety of commercial and household products, such as foam padding, textiles, electronic equipment, airplanes, and automobiles (4). Three commercial formulations, PentaBDE, OctaBDE, and DecaBDE, were used in the United States until 2004 when manufacture of PentaBDE and OctaBDE was phased out because of concerns about toxicity and the bioaccumulation of PBDEs in serum and breast milk (5). DecaBDE was phased out at the end of 2013. In 2010, the US Environmental Protection Agency promulgated rules to further reduce imports of products the contained these chemicals (5). Serum concentrations of PBDEs in the US population in 2003 were the highest reported worldwide (6). Despite increased regulation, the concentrations of the PBDEs in serum increased steadily in the US population (7), but recent evidence suggests that there has been a leveling off and a slight decline, in especially in younger age groups (8).

Only the carcinogenicity of decabromodiphenyl ether (BDE-209, the main congener in the DecaBDE formulation) has been evaluated. Increases in thyroid gland follicular cell adenomas and carcinomas (combined) were observed for male and female mice, and dose-related increases in liver adenomas were found in male and female rats (9). Although considered equivocal by the National Toxicology Program (9), the Environmental Protection Agency considered that these findings indicate carcinogenic potential (10). Long-term studies of the carcinogenicity of the PentaBDEs are ongoing (11).

PBDEs alter thyroid hormone homeostasis in rats and mice (12), resulting in chronic stimulation of the thyroid by thyroid-stimulating hormone, which can increase the incidence of thyroid tumors (13, 14). Although the human thyroid is less sensitive than the rat thyroid to chronic stimulation of thyroid-stimulating hormone (14), emerging evidence from studies of environmental exposure to PBDEs has shown exposure-related disruption of thyroid hormones among men (15–18) and women (19, 20), including both increases (17) and decreases in serum thyroid-stimulating hormone levels (16, 18, 19).

To our knowledge, the association of exposure to PBDEs with thyroid cancer in humans has not been evaluated in any prior studies. We conducted a nested case-control study within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a large multicenter clinical trial in the United States, to evaluate the hypothesis that serum concentrations of PBDEs are associated with thyroid cancer risk.

METHODS

Study population

The study design and sample collection procedures in the PLCO Cancer Screening Trial have been described previously (21, 22). Briefly, PLCO Trial participants ($n = 74,455$) provided nonfasting blood samples at 6 annual medical examinations that occurred between 1992 and 2001 at 10 screening centers (Georgetown University Medical Center, Washington, DC; Henry Ford Health System, Detroit, Michigan; Marshfield Clinical Research Foundation, Marshfield, Wisconsin; Pacific Health Research and Education Institute, Honolulu, Hawaii; University of Alabama at Birmingham, Birmingham, Alabama; University of Colorado, Aurora, Colorado; University of Minnesota, Minneapolis, Minnesota; University of Pittsburgh, Pittsburgh, Pennsylvania; University of Utah, Salt Lake City, Utah, with a satellite in Boise, Idaho; and Washington University, St. Louis, Missouri). Samples were processed and frozen within 2 hours of collection and stored at −70°C.

Cancer incidence was ascertained through 2009. Incident thyroid cancers (*International Classification of Diseases for Oncology, Third Edition*, code 193) were ascertained primarily via annual questionnaires; incident thyroid cancers were also identified through state cancer registries, the National Death Index, physician reports, and next-of-kin reports. Of the breast cancer cases ascertained using these methods, 96.4% were subsequently confirmed by hospital records in a validation project (22). Histologic verification was determined for all thyroid cancers; cases were classified as papillary carcinoma (codes 8050, 8260, 8340–8341, 8343–8344, and 8350; $n = 78$), follicular carcinoma (codes 8290, 8330–8332, and 8335; $n = 17$), medullary carcinoma (codes 8345–8346 and 8510; $n = 3$), anaplastic carcinoma (codes 8012, 8020–8021, and 8030–8032; $n = 2$); and other/unknown (other codes; $n = 4$). Eligible controls for each case were persons who were alive and did not have cancer (with the exception of nonmelanoma skin cancer) at the time of case diagnosis. Two controls were selected for each case and matched according to race, sex, date of birth (within 1 year), center, and date of blood sample (within 15 days). We chose the earliest available serum sample for analysis (median year, 1997). A total of 104 cases and 208 controls were included in the present study. Serum from 1 control was lost because of spillage at the laboratory, which resulted in 104 cases and 207 controls in the analysis. The median time between blood draw and follow-up was 12 years (IQR, 10–13 years; range, 0 (42 days) to 16 (5,772 days) years). All blood samples were collected before cancer diagnosis.

Study activities were approved by the institutional review boards at the National Cancer Institute and the National Center for Environmental Health/Agency for Toxic Substances and Disease Registry of the Centers for Disease Control and Prevention. Review by the Centers for Disease Control and Prevention determined that the National Center for Environmental Health/Agency for Toxic Substances and Disease Registry was not engaged in human subject research. No identifiable personal information was made available to researchers at the Centers for Disease Control and Prevention.

Laboratory analysis of PBDEs

The Centers for Disease Control and Prevention Laboratory for Persistent Organic Pollutants (Atlanta, Georgia) measured 10 tri- to heptabrominated congeners (2,2′,4-tribromodiphenyl ether, 2,4,4′-tribromodiphenyl ether, 2,2′,4,4′-tetrabromodiphenyl ether, 2,3′,4,4′-tetrabromodiphenyl ether, 2,2′,3,4,4′-pentabromodiphenyl ether, 2,2′,4,4′,5-pentabromodiphenyl ether, 2,2′,4,4′,6-pentabromodiphenyl ether, 2,2′,4,4′,5,5′-hexabromodiphenyl ether, 2,2′,4,4′,5,6′-hexabromodiphenyl ether, and 2,2′,3,4,4′,5′,6-hepta-bromodiphenyl ether) (BDE-17, -28, -47, -66, -85, -99, -100, -153, -154, and -183, respectively) in approximately 0.9 g serum using gas chromatography isotope dilution high-resolution mass spectrometry (6). Total lipids were determined based on the measurement of triglycerides and total cholesterol in 0.05 g serum using standard enzymatic methods (Roche Chemicals, Indianapolis, Indiana) (23). PBDE concentrations are expressed as nanograms per gram of blood lipid.

The limits of detection (LODs) for PBDEs ranged between 0.4 ng/g lipids and 2.1 ng/g lipids because of variation in availability of sample volume; the median LODs for individual congeners are shown in Table 1. Laboratory personnel were blinded to case/control status. Internal laboratory quality-control samples included method blanks and laboratory quality-control samples. We prepared additional blinded quality-control samples from stored serum collected from participants of another National Cancer Institute study. Serum was collected in a similar time frame and from participants of a similar age to those in this study. Located in a random order within the 17 batches, we included 13 pairs of duplicates prepared from

Table 1. Lipid-Adjusted Serum Concentrations of Brominated Diphenyl Ether Congeners of Thyroid Cancer Cases ($n = 104$) and Controls ($n = 207$) in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 1992–2009

Congener	Median Limit of Detection[a], ng/g Lipid	No. Detected	% Detected	Cases		Controls		95th Percentile Concentration, ng/g Lipid (Cases)	95th Percentile Concentration, ng/g Lipid (Controls)
				Median	25th–75th Percentile	Median	25th–75th Percentile		
∑PBDEs[b]				12.8	6.6–42.1	19.4	7.6–50.2	525.2	622.1
BDE-17	0.8	13	4.2	<LOD	<LOD–<LOD	<LOD	<LOD–<LOD	<LOD	<LOD
BDE-28	0.8	84	27.0	<LOD	<LOD–0.3	<LOD	<LOD–1.2	14.2	16.3
BDE-47	1.6	292	93.9	8.3	4.3–30.7	12.9	5.1–34.3	302.0	410.0
BDE-66	0.8	15	4.8	<LOD	<LOD–<LOD	<LOD	<LOD–<LOD	<LOD	0.9
BDE-85	0.9	61	19.6	<LOD	<LOD–<LOD	<LOD	<LOD–<LOD	6.9	8.8
BDE-99	1.6	182	58.5	2.0	<LOD–6.1	2.8	<LOD–6.2	108.0	99.5
BDE-100	0.8	204	65.6	1.3	<LOD–5.0	1.7	<LOD–4.7	55.6	76.0
BDE-153	1.0	203	65.3	1.4	<LOD–4.4	1.6	<LOD–3.8	54.2	60.3
BDE-154	0.8	62	19.9	<LOD	<LOD–<LOD	<LOD	<LOD–<LOD	8.6	8.8
BDE-183	1.0	32	10.3	<LOD	<LOD–<LOD	<LOD	<LOD–<LOD	1.6	1.3

Abbreviations: 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-hepta-bromodiphenyl ether; LOD, limit of detection; PBDE, polybrominated diphenyl ether.

[a] Median among cases and controls combined.

[b] Sum of congeners BDE-47, -99, -100, and -153 based on the first imputation for values below the LOD.

13 small serum pools (2 individuals per pool) and 4 pairs of duplicates from a large serum pool. Additionally, we included a single sample from the large serum pool across 7 batches. Detection rates for PBDEs were similar in quality-control and participant samples. We computed the components of the variance using the Proc Varcomp procedure in SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina); between-subject variance was based on controls. Intrabatch coefficients of variation and intraclass correlation coefficients for the lipid-adjusted measurements ranged from 5.6 (BDE-47) to 24.3 (BDE-100) and 97.8% (BDE-100) to 99.9% (BDE-47), respectively. The interbatch variation rounded to 0 for the 4 congeners in our analysis. Concentrations below the LOD for which no signal was detected were imputed from a log-normal probability distribution, which was consistent with the observed distribution of quantified measurements (24). For the imputation procedure, values below the LOD were considered "interval measured," such that the upper bound was equal to the LOD. Values for each interval were imputed from a maximum likelihood regression model that accounted for age, sex, and year of blood draw, assuming a log-normal distribution. The imputation procedure was repeated 5 times.

Statistical analysis

Only 4 PBDE congeners (47, 99, 100, 153) were detected in more than 50% of control samples and were subsequently considered in the analyses. PBDE distributions for cases and controls are shown in Table 1. The sum of the BDEs (∑PBDEs) and BDE-47, BDE-99, BDE-100, and BDE-153 levels were highly correlated (for controls Spearman's $r = 0.70–0.88$; for cases, $r = 0.69–0.90$). We tested case-control differences in distributions by the Wilcoxon signed rank test. We used conditional logistic regression to compute odds ratios and 95% confidence intervals for the association between thyroid cancer and lipid-corrected serum concentrations of PBDEs divided into quartiles (based upon the distribution among controls). We also evaluated uncorrected PBDE concentrations by controlling for serum lipids in the model; results were similar to those for lipid-corrected concentrations, so we present the only the lipid-corrected results. For congeners with more than 25% of data below the LOD (BDE-99, BDE-100, BDE-153), the reference values were those below the LOD, and measured values were divided into tertiles. We also fit conditional logistic models for ∑PBDEs and each BDE congener as continuous variables. Five conditional logistic models were fit using the 5 different imputation data sets. The results were combined using the MIANALYZE procedure in SAS, version 9.2 to create a single odds ratio and 95% confidence interval that accounted for the variability between the imputed values.

Statistical significance was based on a P value <0.05. Tests for trend were calculated by modeling the median BDE concentration in each quartile as a continuous variable. We adjusted the models for years of education (<12 years or ≥12 years), cigarette smoking (never, past, or current), and body mass index (BMI; weight (kg/height (m)^2) (<25, 25–30, or >30) at enrollment. Family history of cancer (any cancer except basal-cell skin cancer) was examined but did not change odds ratios more than 10% (not shown). BMI at 20 years of age, BMI at 50 years of age, and the change in BMI (from the ages of 20 to 50 years) were also examined as potential confounders but did not change odds ratios more than 10% (not shown). We present results for thyroid cancer overall and

Table 2. Lipid-Adjusted Serum Concentrations of Polybrominated Diphenyl Ethers and the Risk of Thyroid Cancer, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 1992–2009

BDE Concentration, ng/g Lipid	All Thyroid Cancers						Papillary Thyroid Cancer					
	Controls	Cases	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI	Controls	Cases	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
∑PBDEs[b]												
Continuous	207	104	0.93	0.80, 1.10	0.94	0.79, 1.11	155	78	0.94	0.79, 1.13	0.96	0.79, 1.17
<LOD–7.6	51	33	1.00		1.00		41	26	1.00		1.00	
7.7–19.4	53	27	0.77	0.41, 1.46	0.66	0.34, 1.30	37	21	0.90	0.44, 1.84	0.82	0.38, 1.77
19.5–50.2	52	21	0.58	0.28, 1.20	0.54	0.24, 1.18	38	12	0.46	0.19, 1.09	0.44	0.17, 1.14
50.3–2,215.0	51	23	0.67	0.33, 1.35	0.62	0.29, 1.30	39	19	0.75	0.34, 1.66	0.76	0.32, 1.61
P for trend			0.51		0.56				0.73		0.87	
BDE-47												
Continuous			0.95	0.81, 1.11	0.95	0.80, 1.12			0.96	0.81, 1.15	0.99	0.81, 1.20
<LOD–5.1	52	33	1.00	Referent	1.00	Referent	44	26	1.00	Referent	1.00	Referent
5.2–12.9	52	26	0.75	0.40, 1.43	0.59	0.30, 1.18	36	20	0.90	0.44, 1.85	0.81	0.38, 1.75
13.0–34.3	52	23	0.65	0.32, 1.34	0.56	0.26, 1.23	34	13	0.62	0.27, 1.45	0.60	0.24, 1.52
34.4–1,130.0	51	22	0.65	0.32, 1.30	0.56	0.27, 1.19	41	19	0.76	0.35, 1.66	0.75	0.32, 1.73
P for trend			0.42		0.46				0.63		0.74	
BDE-99												
Continuous			0.95	0.82, 1.10	0.95	0.81, 1.11			0.96	0.82, 1.12	0.97	0.81, 1.16
<LOD	81	48	1.00	Referent	1.00	Referent	64	38	1.00	Referent	1.00	Referent
>LOD–3.6	42	15	0.58	0.28, 1.20	0.48	0.21, 1.07	26	9	0.58	0.24, 1.40	0.51	0.20, 1.32
3.7–9.8	43	21	0.80	0.41, 1.55	0.78	0.38, 1.61	35	14	0.66	0.31, 1.42	0.71	0.31, 1.64
9.9–378.0	41	20	0.80	0.42, 1.54	0.79	0.40, 1.57	30	17	0.93	0.45, 1.91	0.98	0.46, 2.10
P for trend			0.82		0.90				0.79		0.67	
BDE-100												
Continuous			0.97	0.86, 1.09	0.96	0.84, 1.09			0.99	0.86, 1.13	1.00	0.86, 1.16
<LOD	66	41	1.00	Referent	1.00	Referent	53	31	1.00	Referent	1.00	Referent
>LOD–2.1	47	23	0.72	0.36, 1.46	0.48	0.22, 1.05	33	18	0.90	0.40, 2.01	0.68	0.28, 1.66
2.2–6.0	48	15	0.43	0.19, 0.95	0.39	0.17, 0.89	34	9	0.45	0.18, 1.09	0.47	0.19, 1.19
6.1–289.0	46	25	0.83	0.43, 1.60	0.70	0.34, 1.42	35	20	0.95	0.44, 2.05	0.93	0.40, 2.13
P for trend			0.89		0.90				0.73		0.59	
BDE-153												
Continuous			0.95	0.82, 1.10	0.96	0.82, 1.11			0.94	0.79, 1.12	0.96	0.79, 1.15
<LOD	66	42	1.00	Referent	1.00	Referent	50	33	1.00	Referent	1.00	Referent
>LOD–1.8	49	21	0.59	0.29, 1.19	0.62	0.31, 1.26	37	15	0.53	0.23, 1.19	0.58	0.25, 1.32
1.9–4.7	46	17	0.53	0.25, 1.09	0.48	0.22, 1.05	33	12	0.52	0.23, 1.17	0.48	0.20, 1.17
4.8–418.0	46	24	0.75	0.39, 1.44	0.76	0.38, 1.51	35	18	0.71	0.33, 1.52	0.78	0.35, 1.75
P for trend			0.97		0.97				0.90		0.89	

Abbreviations: BDE-47, 2,2′,4,4′-tetrabromodiphenyl 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; CI, confidence interval; LOD, limit of detection; OR, odds ratio; PBDE, polybrominated diphenyl ether.

[a] Odds ratios were adjusted for years of education (<12 years vs. ≥12 years), cigarette smoking (never, past, or current), and body mass index (weight (kg)/height $(m)^2$; <25, 25–30, or >30).

[b] Sum of congeners BDE-47, -99, -100, and -153 based on the first imputation for values below the LOD.

separately for the papillary subtype. We stratified our results by sex, age, smoking status, and BMI to consider effect modification. We also evaluated potential indicators of iodine sufficiency, including energy-adjusted total seafood and total dairy intakes (below and at or above the median intake), among a subset of 94 cases and 187 matched controls who completed the food frequency questionnaire.

RESULTS

Cases were more likely to be never smokers and currently married and to have a higher BMI than were controls (data not shown). The average age of the cases and controls was 61.8 years; 65% were women and 87% white. Levels of ∑PBDEs ranged from 1.2 ng/g lipid to 2,215 ng/g lipid among controls. The cases and controls had similar percentages of detections of the BDEs (Table 1). The congener with the highest median concentration (ng/g lipid) was BDE-47 (among controls median, 12.9 ng/g, IQR, 5.1–34.3), followed by BDE-99 (median, 2.8 ng/g, IQR, (<LOD–6.2), BDE-100 (median, 1.7 ng/g, IQR: <LOD–4.7), and BDE-153 (median, 1.6 ng/g, IQR, <LOD–3.8). BDE-47 represented an average of 70.5% of ∑PBDEs; percentages were 9.3%, 7.5%, and 10.2% for BDE-99, BDE-100, and BDE-153, respectively. There were no significant differences between cases and controls in lipid-corrected concentrations of ∑PBDEs or of the individual congeners.

Increasing quartiles of ∑PBDEs, BDE-47, BDE-99, BDE-100, and BDE-153 were not associated with risk of thyroid cancer overall (Table 2). Adjustment for educational level, smoking status, and BMI had little effect on the risk estimates. Restricting our analyses to cases with the papillary subtype did not alter the findings. We did not observe any effect modification by sex, median BMI, total seafood intake (≤50th percentile vs. >50th percentile), or total dairy intake (≤50th percentile vs. >50th percentile) (data not shown). Excluding subjects with blood draws less than 1 year before diagnosis (5 cases and 10 matched controls) or missing diagnosis year (2 cases and 4 matched controls) did not significantly change risk estimates (results not shown).

DISCUSSION

In the present nested case-control study, we found no association between serum levels of BDEs and the risk of thyroid cancer. Results were similar for men and women and for papillary thyroid cancer, which constituted 75% of all thyroid cancers in our study.

The average levels of BDE-47 in our study population (among controls, mean = 69.2 ng/g lipid) were slightly higher than levels in the 2003–2004 and 2005–2006 National Health and Nutrition Examination Surveys in the ≥60 year age group (means = 52 and 61 ng/g lipid, respectively) (8) and another study from the early 2000s (6).

To our knowledge, there have been no prior population-based studies that have evaluated blood levels of PBDEs and the risk of thyroid cancer. Our study has several strengths. Disease status could not have biased the results because serum samples were collected from participants before diagnosis. We used an established analytical method to measure PBDEs and corrected values for serum lipids. Limitations included low case numbers, particularly for analyses stratified by sex and restricted to the papillary type, and potentially inadequate follow-up time. The generalizability of our study is also a limitation because our study population was older, with an average age of 62 years, and thyroid cancer is most frequently diagnosed among people 40–59 years of age (1). Another potential limitation is the use of 1 serum sample to characterize exposure. If levels changed over time, 1 sample might not be able to adequately characterize exposure, and the resulting misclassification would be likely to attenuate risk estimates. The lack of data on PBDE-209, a congener for which carcinogenicity has been assessed (10), is also a limitation of our study. In addition, detection bias from screening practices (25) might have led to increasing incidence because of greater detection of small thyroid tumors, although it is unlikely that this would bias the association between PBDEs and thyroid cancer.

Despite the demonstrated disruption of thyroid homeostasis by environmental levels of PBDEs, including levels similar to those we observed in this study population, our study of a modest number of cases does not provide support for an increased risk of thyroid cancer associated with exposure to PBDEs.

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REFERENCES

1. Kilfoy BA, Devesa SS, Ward MH, et al. Gender is an age-specific effect modifier for papillary cancers of the thyroid gland. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1092–1100.
2. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Limited-Use, Nov 20013 Sub (1973–2011)—Linked To County Attributes—Total U.S., 1969–2012 Counties. Surveillance Research Program, Cancer Statistics Branch,

National Cancer Institute. Data submitted November 2013. Released April 2014.
3. Kilfoy BA, Zheng T, Holford TR, et al. International patterns and trends in thyroid cancer incidence, 1973–2002. *Cancer Causes Control*. 2009;20(5):525–531.
4. Birnbaum LS, Staskal DF. Brominated flame retardants: cause for concern? *Environ Health Perspect*. 2004;112(1):9–17.
5. US Environmental Protection Agency. Technical Fact Sheet—Polybrominated Diphenyl Ethers (PBDEs) and Polybrominated Biphenyls (PBBs). http://www2.epa.gov/fedfac/technical-fact-sheet-polybrominated-diphenyl-ethers-pbdes-and-polybrominated-biphenyls-pbbs. Published January 2014. Accessed September 24, 2014.
6. Schecter A, Päpke O, Tung KC, et al. Polybrominated diphenyl ether flame retardants in the U.S. population: current levels, temporal trends, and comparison with dioxins, dibenzofurans, and polychlorinated biphenyls. *J Occup Environ Med*. 2005; 47(3):199–211.
7. Sjödin A, Patterson DG Jr, Bergman A. A review on human exposure to brominated flame retardants—particularly polybrominated diphenyl ethers. *Environ Int*. 2003;29(6): 829–839.
8. Sjödin A, Jones RS, Caudill SP, et al. Polybrominated diphenyl ethers, polychlorinated biphenyls, and persistent pesticides in serum from the National Health and Nutrition Examination Survey: 2003–2008. *Environ Sci Technol*. 2014;48(1): 753–760.
9. NTP. *Toxicology and carcinogenesis studies of decabromodiphenyl oxide (CAS No. 1163–19-5) in F344/N rats and B6C3F1 mice (feed studies)*. Research Triangle Park, NC: National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health; 1986. (NTP Technical Report 309: NIH publication no. 86-2565). http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr309.pdf. Accessed September 24, 2014.
10. EPA IRIS. Toxicological review of decabromodiphenyl ether (BDE-209) in support of summary information on the Integrated Risk Information System. 2008. (EPA 635-R-07-008F). www.epa.gov/ncea/iris/toxreviews/0035tr.pdf. Accessed September 24, 2014.
11. NTP. National Toxicology Program. http://ntp.niehs.nih.gov. Accessed September 24, 2014.
12. Darnerud PO. Toxic effects of brominated flame retardants in man and in wildlife. *Environ Int*. 2003;29(6):841–853.
13. Zhao L, Zhu X, Won Park J, et al. Role of TSH in the spontaneous development of asymmetrical thyroid carcinoma in mice with a targeted mutation in a single allele of the thyroid hormone-β receptor. *Endocrinology*. 2012;153(10): 5090–5100.
14. Capen CC. Pathophysiology of chemical injury of the thyroid gland. *Toxicol Lett*. 1992;64-65(Spec No.):381–388.
15. Meeker JD, Johnson PI, Camann D, et al. Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men. *Sci Total Environ*. 2009;407(10): 3425–3429.
16. Turyk ME, Persky VW, Imm P, et al. Hormone disruption by PBDEs in adult male sport fish consumers. *Environ Health Perspect*. 2008;116(12):1635–1641.
17. Johnson PI, Stapleton HM, Mukherjee B, et al. Associations between brominated flame retardants in house dust and hormone levels in men. *Sci Total Environ*. 2013;445-446: 177–184.
18. Wang H, Zhang Y, Liu Q, et al. Examining the relationship between brominated flame retardants (BFR) exposure and changes of thyroid hormone levels around e-waste dismantling sites. *Int J Hyg Environ Health*. 2010;213(5):369–380.
19. Chevrier J, Harley KG, Bradman A, et al. Polybrominated diphenyl ether (PBDE) flame retardants and thyroid hormone during pregnancy. *Environ Health Perspect*. 2010;118(10): 1444–1449.
20. Stapleton HM, Eagle S, Anthopolos R, et al. Associations between polybrominated diphenyl ether (PBDE) flame retardants, phenolic metabolites, and thyroid hormones during pregnancy. *Environ Health Perspect*. 2011;119(10): 1454–1459.
21. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000;21(6 Suppl): 273S–309S.
22. Hayes RB, Reding D, Kopp W, et al. Etiologic and early marker studies in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000;21(6 Suppl): 349S–355S.
23. Phillips DL, Pirkle JL, Burse VW, et al. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. *Arch Environ Contam Toxicol*. 1989;18(4):495–500.
24. Lubin JH, Colt JS, Camann D, et al. Epidemiologic evaluation of measurement data in the presence of detection limits. *Environ Health Perspect*. 2004;112(17):1691–1696.
25. Brito JP, Davies L. Is there really an increased incidence of thyroid cancer? *Curr Opin Endocrinol Diabetes Obes*. 2014; 21(5):405–408.