Polybrominated Diphenyl Ethers, Thyroid Hormones, and Risk of Papillary Thyroid Cancer

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Abstract

Polybrominated Diphenyl Ethers, Thyroid Hormones, and Risk of Papillary Thyroid Cancer

Huang Huang

2021

Thyroid cancer is the most common cancer of the endocrine system. The incidence of thyroid cancer has increased worldwide for decades in the general populations and in the US military personnel. Although emerging evidence indicates that exposure to polybrominated diphenyl ethers (PBDEs) is related to disruption of thyroid hormone homeostasis, the association between exposure to PBDEs and risk of thyroid cancer is still unclear. Additionally, mutations in genes coding for enzymes involved in regulation, metabolism, or functional activation of PBDEs and thyroid hormones could modify the PBDEs and thyroid hormones related risk of thyroid carcinogenesis. Using data from a nested case-control study including 742 pairs of papillary thyroid cancer (PTC) cases and individually matched controls with pre-diagnostic serum concentrations of PBDEs and thyroid hormones from the Department of Defense Serum Repository (DoDSR), we tested the hypothesis that exposure to elevated PBDEs increases the risk of PTC and the increased risk posed by PBDEs is through the disruption of thyroid hormones. We also investigated the effects of genetic variants in genes involved in metabolism/detoxification of PBDEs and thyroid hormones on the association between PBDEs, thyroid hormones, and risk of PTC. Results from this study suggested that exposure to BDE-28 and dysregulate serum levels of thyroid stimulating hormone (TSH) were associated with increased risk of PTC. This study also observed significantly nonmonotonic relationships between serum concentrations of BDE-153 and 2,2’,4,4’,5,5’-hexabromobiphenyl (BB-153) and serum levels of total triiodothyronine (TT3) and total thyroxine (TT4) in PTC cases, and between BDE-47, -100, and -153 in relation to free T4 (FT4) level in controls. However, results from the causal mediation analysis did not support the hypothesis that thyroid carcinogenesis of PBDEs is mainly operated through disruption of thyroid hormone homeostasis. Investigation on
the genetic polymorphisms and gene-environment interactions suggested significant interactions between BDE-28 and single nucleotide variants (SNVs) on CYP2E1 rs7092584 and DIO2 rs12885300. Serum level of TSH also interacted with UGT1A rs1875263, DIO2 rs1288530, and UGT1A rs2011404. Findings of this study provides evidence to the link between exposure to PBDEs and risk of PTC, which will promote further regulations on production and application of PBDEs. Also, there could be significant clinical implications to monitor and regulate thyroid hormone levels among the most susceptible populations. Results from the gene-environment interaction analysis provide novel evidence to understand the basis of the molecular biology behind the initiation and promotion of PTC. With further understanding the pathogenesis of PTC, as well as implementing appropriate regulation and intervention, it should be pursued to decrease the incidence of PTC in the public, and to reduce the health and economic burdens caused by thyroid cancer.
Polybrominated Diphenyl Ethers, Thyroid Hormones, and Risk of Papillary Thyroid Cancer

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Table of Contents

Introduction.................................................................................................................................................. 1
Polybrominated Diphenyl Ethers, Polybrominated Biphenyls, and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study ......................................................................................................................... 5
Thyroid-Stimulating Hormone, Thyroid Hormones, and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study ................................................................................................................................................. 41
Polybrominated Diphenyl Ethers, Polybrominated Biphenyls, and Peripheral Circulating Levels of Thyroid Hormones in Relation to Risk of Papillary Thyroid Cancer: A Nested Case-Control Study ........................................................................................................................................... 64
Genetic Polymorphisms in Phase I and Phase II Metabolism/Detoxification and Thyroid Hormone Metabolism Pathways, Polybrominated Diphenyl Ethers, Thyroid-Stimulating Hormones, and Risk of Papillary Thyroid Cancer .............................................................................................................................. 102
Conclusion ..................................................................................................................................................... 149
References ..................................................................................................................................................... 152
INTRODUCTION

Thyroid cancer is the most common cancer of the endocrine system. The age-adjusted incidence rates of thyroid cancer have increased worldwide for decades and have been increasing faster than any other malignancies [1-4]. The incidence of thyroid cancer increased by 148% among men (from 3.1 to 7.7 per 100,000 persons) and 247% among women (from 6.4 to 22.2 per 100,000 persons) in the US between 1975 and 2014 [5]. Most of the increased incidence is in papillary thyroid cancer (PTC), which is the most common histologic type and accounts for more than 80% of all thyroid carcinomas [6, 7]. A pattern of increasing rates was also observed in the US military personnel. The incidence of papillary thyroid cancer increased from 2.52 to 2.76 per 100,000 persons among servicemen and from 13.31 to 19.64 among servicewomen between the periods 1990-1997 and 1998-2004 [8]. Additionally, the incidence was significantly higher in servicewomen than women in the general population for ages 20-49 years when thyroid cancer risk is at its highest [8, 9].

Etiologic factors underlying thyroid cancer are poorly understood. The most well-established risk factors include age, female gender, exposure to ionizing radiation, history of benign thyroid disease, and family history of thyroid cancer [10-13]. Recent studies have also identified higher body weight and height [14, 15] and insulin resistance syndrome [16] as risk factors. While the advanced medical surveillance and diagnostic technology have enhanced diagnosis rate of thyroid cancer, emerging environmental chemicals or physical agents have also been suggested to contribute to the increasing trend of incidence [17-19].

Since 1970s, polybrominated diphenyl ethers (PBDEs) have been widely used as flame retardants in a variety of commercial and household products, including plastics, furniture, upholstery, textiles, electrical equipment, and electronic devices [20]. Commercial PBDEs are usually present as mixtures of various congeners combined in different percentages. Because PBDEs are physically
mixed into products as additives, rather than chemically bond with polymer resins, they have a potential to release into environment through production process or from products usage [21]. The environmental PBDEs are persistent, with degradation half-lives in the order of years [22]. Due to their high lipophilicity, PBDEs could also bioaccumulate and be biomagnified through food chains [23, 24]. Humans could be exposed to environmental PBDEs via inhalation, dust ingestion, and dietary intake [20, 25].

The environment and human body burdens of PBDEs have been increasing rapidly worldwide in the last few decades. An approximately 100-fold increased levels of PBDEs in human populations have been noticed from 1970 to 2002 [26]. Despite concerns about increasing exposure and potential adverse health effects (e.g., immunotoxicity, endocrine disruption, and adverse effects on neurological development and reproductive system [25, 27-31]), the US government did not implement any regulations on PBDEs until 2004 [32, 33], and the prohibition on PBDEs only enacted in 10 US states so far [33]. Even with increased regulation, PBDEs remain ubiquitous in environment due to their persistence and bioaccumulation [19, 20]. Although some investigations suggest a moderate decline of PBDE body burdens approximately after 2000 [33, 34], others have reported a significant increase of several PBDE congeners from 2011 to 2015 [32, 35]. 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 [32, 34].

Emerging evidence indicates that exposure to PBDEs is related to disruption of thyroid hormone homeostasis [36-38]. Since the chemical structures of PBDE congeners are similar to those of thyroid hormones (i.e., triiodothyronine [T3] and thyroxine [T4]), the hydroxylated metabolites of PBDE congeners could competitively bind to thyroid hormone transport proteins and receptors [19]. Additionally, PBDEs can induce the activity of major thyroid hormone metabolic enzymes, including cytochrome P450 isozymes (CYPs), uridine 5'-diphospho-glucuronosyltransferases
(UDP GTs), sulfotransferases (SULTs), and deiodinases [19]. Thus, PBDEs can affect the distribution and metabolism of T3 and T4. The disruption of thyroid hormone homeostasis could further influence the secretion of thyroid stimulating hormone (TSH) through a negative feedback loop on the hypothalamus-pituitary-thyroid axis.

Although the association between exposure to PBDEs and risk of thyroid cancer is still unclear, it is biologically possible that PBDEs can increase the risk of thyroid cancer through disruption of thyroid hormone homeostasis. Since TSH plays an essential role in regulating thyroid function and increasing thyroid cell proliferation [39], thyroid carcinogenesis can be caused by fluctuation of TSH level or disruption of thyroid hormone homeostasis, which inversely regulates the secretion of TSH. The associations between dysregulation of TSH and thyroid hormones and risk of thyroid cancer have been suggested by several previous epidemiological studies [40-42]. However, there is still lacking evidence neither on association between PBDEs and risk of thyroid cancer nor on potential mediation effect of TSH and thyroid hormones on this association. Animal studies of carcinogenic effects of PBDEs are limited to deca-brominated diphenyl ethers (deca-BDEs). These studies reported a slightly elevated incidence of thyroid gland adenoma or carcinoma (combined) and a significantly increased incidence of follicular cell hyperplasia, which is considered as a precursor of thyroid tumors, in exposed mice [20]. Thus far, only three epidemiological studies have investigated the relationship between exposure to PBDEs and risk of thyroid cancer and have reached inconsistent results. A population-based case-control study from Connecticut reported some suggestive evidence of an inverse association between serum level of BDE-209 and PTC in 250 female cases and 250 female controls frequency matched on age [43], while one hospital-based case-control study investigated PBDEs in house dust and serum samples of 70 PTC cases and 70 non-cancer controls, and reported a positive association with the dust level of BDE-209 [44]. Another nested case-control study including 104 incident thyroid cancer cases and 208 individually
matched controls from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Cohort did not find any associations [45].

Based on the biologically possible effects of PBDEs and thyroid hormones on the risk of thyroid cancer, mutations in genes coding for enzymes involved in regulation, metabolism, or functional activation of PBDEs and thyroid hormones could modify the PBDEs and thyroid hormones related risk of thyroid carcinogenesis. Some genes involved in metabolism/detoxification enzymes (e.g., \textit{CYP1A1}, \textit{CYP2D6}, \textit{CYP2E1}, \textit{GSTM1}, and \textit{GSTT1}) have been suggested to be associated with thyroid cancer [46-49]. One study examined the modification effects of genetic variants in metabolism/detoxification pathways on the associations between tobacco and alcohol use and risk of PTC, and reported significant interactions between \textit{CYP26B1} and cigarette smoking and between \textit{UGT2B7} and alcohol consumption [50]. However, no study has investigated the effects of genetic polymorphisms on the association between environmental chemicals and thyroid cancer.

Using data from a nested case-control study including 742 pairs of PTC cases and individually matched controls with pre-diagnostic serum concentrations of PBDEs and thyroid hormones from the Department of Defense Serum Repository (DoDSR), we tested the hypothesis that exposure to elevated PBDEs increases the risk of PTC and the increased risk posed by PBDEs is through the disruption of thyroid hormones. We also investigated the effects of genetic variants in genes involved in metabolism/detoxification of PBDEs and thyroid hormones on the association between PBDEs, thyroid hormones, and risk of PTC.
Polybrominated Diphenyl Ethers, Polybrominated Biphenyls, and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study

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Abstract

Background: A nested case-control study was carried out using data from the Department of Defense cohort to investigate the associations of papillary thyroid cancer (PTC) with serum concentrations of polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs).

Methods: This study included 742 (341 women and 401 men) histologically confirmed PTC cases and 742 matched controls with pre-diagnostic serum samples from the Department of Defense Serum Repository. Lipid-corrected serum concentrations of seven PBDE congeners and one PBB congener were measured. Multivariate conditional logistic regression analyses were performed for classical PTC and follicular variant of PTC, respectively. We also examined effect modification by gender.

Results: BDE-28 was associated with significantly increased risk of classical PTC [OR=2.09; 95% CI, 1.05, 4.15, for the 3rd tertile vs. below limit of detection; P_trend=0.02] adjusting for other congeners, body mass index, and branch of military service. This association was mainly observed for larger classical PTC (tumor size >10 mm) with a significantly stronger association among women than men (P_interaction=0.004). No consistent associations were observed for other PBDE and PBB congeners, including those at higher concentrations.

Conclusions: This study found a significantly increased risk of classical PTC associated with increasing levels of BDE-28. The risk varied by gender and tumor size.

Keywords: polybrominated diphenyl ethers, PBDEs, polybrominated biphenyls, PBBs, papillary thyroid cancer
Thyroid cancer is the most prevalent cancer of the endocrine system, and its incidence has been increasing faster than 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 [5]. A pattern of increasing rates was also observed in the 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 [51]. The majority of increase is in papillary thyroid cancer (PTC), which is the most common histologic type and accounts for more than 80% of all thyroid carcinomas [6, 7]. While the increased detection of occult disease has contributed to the increasing trend, environmental chemicals or physical agents have also been suggested to play a role [18, 19, 52].

Since 1970s, polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs) have been widely used as flame retardants in the US general and military population in a variety of commercial and household products, including plastics, furniture, upholstery, textiles, electrical equipment, and electronic devices [40, 41]. Since PBDEs and PBBs are physically mixed into products, they have the potential to release into the environment and enter the human body [40, 41]. The environmental and human levels of PBDEs have been increasing rapidly in the last three decades [19]. Due to concerns about increasing exposure and potential adverse health effects, the US government banned the production of PBBs in 1976 increased regulations on PBDEs in 2004 [53, 54]. Despite this, PBDEs and PBBs remain ubiquitous in the environment and are being detected in human populations due to their persistence and bioaccumulation [19, 41]. Among Michigan women exposed to PBBs in an accidental contamination of food supply (1973-1974), their blood concentrations of PBB-153 in 2004 were still substantially higher as compared with the National Health and Nutrition Examination Survey (NHANES) data 2003-2004 [55, 56]. Although
some investigations on temporal trends of PBDE body burdens suggest a moderate decline starting
approximately after 2000 [54, 57], others have reported a significant increase of several PBDE
congeners from 2011-2015 [53, 58]. 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 [53, 57].

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 [59, 60], but
epidemiological studies have yielded conflicting findings in the associations between PBDE and
PBB exposures and thyroid function [55, 61-63].

Animal studies of carcinogenic effects of PBDEs are limited to deca-brominated diphenyl ethers
(BDE). 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 as a precursor of thyroid tumors, in exposed mice [40]. To our knowledge, only three
epidemiological 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 [44], while another two studies, one including 104 cases and 207 controls and the
other including 250 female cases and 250 female controls, did not find any positive association
with PBDEs or PBBs [43, 45].

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

Methods

Study population

Detailed information regarding the study design has been described [64]. In brief, 742 pairs of PTC cases and controls were selected from US military personnel who had serum samples stored in the DoDSR. Serum samples from all military members were drawn during active duty. Inclusion criteria for cases: (i) histologically confirmed (ICD-O-3: 8050, 8260, and 8340-8343); (ii) at least three 0.5-mL pre-diagnostic (total 1.5 mL) and one 0.5-mL post-diagnostic serum samples stored in the DoDSR since 1989; (iii) diagnosis between 2000 and 2013; (iv) age 21 years or older at diagnosis, and (v) without any cancers (except for non-melanoma skin cancer) prior to the date of PTC diagnosis. Controls who had no diagnosis with any cancer (except for non-melanoma skin cancer) were randomly selected and individually matched to cases on date of birth (±1 year), gender, race/ethnicity, and midpoint of dates of the selected four samples drawn (±1 year). Demographic and military characteristics for all participants were abstracted from the DMSS. All study procedures were approved by the Uniformed Services University Institutional Review Board, the Walter Reed National Military Medical Center, the DoD Joint Pathology Center, and the Human Investigation Committee of Yale University. The involvement of the Centers for Disease Control and Prevention (CDC) 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 pre-diagnostic serum sample. The measurement was conducted at the Persistent Organic Pollutants Laboratory, CDC (Atlanta, Georgia). The methodology used has been published [65]. Briefly, the serum samples were at first automatically fortified with internal standards using Gilson 215 liquid handler (Gilson,
Inc.; Middleton, WI). The samples were then extracted by automated liquid-liquid extraction (LLE) using a liquid handler. Removal of co-extracted lipids were performed on a silica: silica/sulfuric acid column using the Rapid Trace (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 (GC-ID/HRMS) employing a DFSTM (Thermo DFS, Bremen, Germany) 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 one 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 χ² tests ranged 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 (p-values from the Mann-Whitney U tests ranged 0.14-0.74). We also examined the distributions of concentrations by participants’ demographic characteristics and military services, and summarized the results in Supplementary Tables 1 and 2.

Statistical analyses

The distributions of demographic and military characteristics were compared between cases and controls using the χ² test. Since 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, seven 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 five congeners with ≤25% of data below the limits of detection (LODs) (BDE-47, -99, -100, -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 employed to estimate the associations between risk of PTC and levels of PBDE and PBB congeners. We applied two approaches: single chemical models and multi-chemical models. Both single and multi-chemical models were 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 multi-chemical model, we included all the categorical PBDE and PBB congeners in one model to additionally control for potential confounding effects from other congeners. Given that the categorized congeners were not highly correlated (Cramer's Vs ranged 0.05-0.73; Supplementary Table 3), the estimated associations are not likely to be affected by multicollinearity.

Statistical analyses were performed for histologic subtype, classical PTC (ICD-O-3: 8050, 8260, 8341-8343) and follicular variant of PTC (ICD-O-3: 8340), respectively. Further stratified analyses were conducted by tumor size (classical PTC microcarcinoma with tumor size ≤10 mm and large classical PTC with tumor size >10 mm) and then by gender 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 [66]. The remaining participants were stratified by tumor size and each cut-point of years between the time of serum sample collection and PTC diagnosis (5-12 years) to evaluate if the timing of sample collection modified the associations.

Since a variety of PBDE congeners usually exist in a certain product, exposure to one congener is likely to be correlated with exposure to others that containing in the same product. The high correlation between PBDE congeners could lead to an issue of multicollinearity, which confounds the estimated effect of each congener on risk of PTC. Thus, the estimates from single- and multiple-chemical conditional logistic regression models are further confirmed by performing alternative statistical methods, including principal component analysis (PCA) and conditional logistic regression with elastic net penalties, to avoid the effect of multicollinearity. The principal components created by PCA are included in one conditional logistic regression model to test their associations with risk of PTC.

All tests were 2-sided with \( \alpha=0.05 \). Since seven PBDE and one PBB congeners were included in the final analysis, a Bonferroni adjusted \( \alpha \) of 0.05/8=0.006 was applied to control for multiple comparisons. Because single and multi-chemical models provided similar risk estimates, all results are presented from the multi-chemical models. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc.; Cary, NC).

**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, gender, 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 from 1994-2009 and between 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, with interquartile range (IQR) from 21-32 years.

An elevated risk of classical PTC was associated with higher levels of BDE-28 (OR=2.09; 95% CI, 1.05, 4.15 for the 3rd tertile vs. <LOD; \( P_{\text{trend}}=0.020 \)) (Table 3), although the \( P_{\text{trend}} \) was no longer significant after the Bonferroni adjustment. A borderline significantly reduced OR was observed for the 2nd 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 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 (OR=2.35; 95% CI, 1.15, 4.80 for the 2nd tertile vs. <LOD; OR=4.77; 95% CI, 1.84, 12.35 for the 3rd tertile vs. <LOD; \( P_{\text{trend}}=0.0014 \)) (Table 4). The \( P_{\text{trend}} \) remained significant after the Bonferroni adjustment. There were significantly increased ORs for large classical PTC with BDE-154 for the 1st and 2nd tertiles vs. <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 3rd tertile vs. <LOD (\( P_{\text{trend}}=0.039 \)). For classical PTC microcarcinoma, there were significantly decreased ORs with BDE-154 for the 2nd and 3rd tertiles vs. <LOD (OR=0.15; 95% CI, 0.02, 0.93 and OR=0.04; 95% CI, 0.003, 0.51, respectively; \( P_{\text{trend}}=0.017 \)). A significantly
reduced OR was also observed for large classical PTC with the 2nd 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 neither large classical PTC nor classical PTC microcarcinoma.

Gender 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 (OR=10.74; 95% CI, 1.93, 59.72 for the 3rd tertile vs. <LOD; P_trend=0.0054) than men (OR=3.39; 95% CI, 0.98, 11.71 for the 3rd tertile vs. <LOD; P_trend=0.071; P_interaction=0.0040). After Bonferroni adjustment, the P_trend remained significant only among women, and the effect modification by gender remained significant. No significant association was observed for the other PBDE and PBB congeners among either men or women. The null associations between levels of BDE-28 and risk of classical PTC microcarcinoma were among both men and women (Supplementary 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 (OR=1.80; 95% CI, 1.00, 3.21 for the 2nd tertile vs. <LOD; OR=2.53; 95% CI, 1.19, 5.36 for the 3rd tertile vs. <LOD; P_trend=0.014) (Supplementary 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).

Results from the PCA suggested that the first component was associated with an increased risk of classical PTC (OR=1.96; 95% CI: 1.00, 1.12; P=0.043) (Supplementary Table 6). According to the eigenvector values, all PBDE congeners, except BDE-153, were almost equally correlated with this
component (eigenvectors ranged 0.3785-0.3971), which may suggest that PBDEs as a mixture is associated with increased risk of classical PTC. BDE-28 was the dominant congener in the third component. Increased value of the third component was mainly associated with decreased BDE-28. Since the point estimate of OR was less than 1 with this component, this result may support a positive association between BDE-28 and risk of classical PTC.

The penalized conditional logistic regression was conducted by including a penalty parameter in the multiple-chemical conditional logistic regression. When pure Lasso and pure ridge were used as penalty parameters, the ridge traces suggested that BDE-28 had the largest risk effect, while BDE-100 had the greatest protective effect, on the risk of classical PTC. Also, these effects were less influenced by collinearity between other congeners (Supplementary Figure 1). These results were consistent with findings that BDE-28 was associated with an increased risk of PTC.

**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 mainly observed for classical PTC among cases with tumor size >10 mm, and was stronger among women.

The geometric means of concentrations for BDE-28, -47, -99, -100, -153, and BB-153 in controls of this study were higher than those in the US general population from the NHANES 2003-2004 [56]. 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 2003/04 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 2003/04 population, indicating a more centralized range of concentrations in the current military population as compared
to the NHANES general population. A similar range of concentrations was only observed for BDE-153 between the study population and NHANES 2003/04 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. Since 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 [19]. Additionally, PBDEs can induce thyroid hormone metabolic enzyme activity [19]. These two potential mechanisms suggested PBDEs and PBBs could disrupt thyroid hormone homeostasis and could contribute to cancer risk and severity [44].

A recent prospective cohort study [67] reported that significant decrements in thyroid stimulating hormone (TSH) 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 TSH among females. Since there is an indication from two other prospective cohort studies [64, 68] that lower TSH levels 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 TSH.

Although the latency period between chemical exposure and appearance of thyroid cancer is still unclear, a 5-10 years latency period has been reported for thyroid cancer after radiation exposure [66]. 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 three epidemiological 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 non-cancer controls [44]. 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. A nested case-control study including 104 incident thyroid cancer cases and 207 matched controls in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial Cohort reported no association between PBDEs and risk of thyroid cancer [45]. 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. Another population-based case-control study including 250 female cases and 250 female controls from Connecticut also did not find any positive association between PBDEs and PTC [43]. The lower serum concentrations of PBDEs in Connecticut women as compared to those in ours and other populations may contribute to the observed null associations.

BDE-28 mainly exists in the penta-BDE commercial mixture [53], 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 2008/09 to 2011/12, flattened between 2011/12 and 2014, and then increasing in 2014, among pregnant women in California [53]. This recently increasing trend of BDE-28 may be due to the debromination of the higher brominated congeners [53], but still need to 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 gender, which is important because women are approximately three times more likely to develop thyroid cancer than men. The study population was composed entirely of US active-duty military personnel, a younger population
represents the age groups at which thyroid cancer risk is at its highest. Additionally, the single-payer universal (i.e., equal access) military healthcare 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-lives range between 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 DoDSR 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, history of benign thyroid disease, and a family history of thyroid cancer. There were also a high percentage of participants with missing BMI data, which may have led to insufficient adjustment for BMI. Previous evidence has suggested lower prevalence of obesity and larger lean body mass of military personnel than the US civilian population [69], indicating less variation of BMI among the US military personnel. Thus, any effect of under-adjustment for 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 variation of PTC may 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 the 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. Since a recent study reported an
increasing trend of BDE-28 concentrations in the serum of pregnant women in California between 2008-2014 [53], and accumulative evidence has suggested potential adverse effects on the thyroid for PBDE alternatives [44, 70], further investigation into the association between BDE-28, other PBDE congeners and alternatives, and thyroid cancer is warranted. Additionally, more epidemiological studies among different populations are also warranted to confirm these findings and identify high risk populations who are susceptible to these chemicals.
Acknowledgments

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Conflict of interest
The authors declare they have no actual or potential conflict of interests.

Disclaimer
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Uniformed Services University of the Health Sciences, the Department of Defense, or the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the Department of Defense, the CDC, the Public Health Service, or the US Department of Health and Human Services.
Table 1. Lipid-corrected serum concentrations of PBDE and PBB congeners (ng/g) among PTC cases and controls.

<table>
<thead>
<tr>
<th>Congener</th>
<th>Median LOD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Detected No. (%)</th>
<th>Geometric Mean (GSD)</th>
<th>Median (IQR)</th>
<th>Detected No. (%)</th>
<th>Geometric Mean (GSD)</th>
<th>Median (IQR)</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDE-17</td>
<td>1.0</td>
<td>41 (5.5)</td>
<td>2.1 (2.0)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>30 (4.0)</td>
<td>1.9 (1.9)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>0.18</td>
</tr>
<tr>
<td>BDE-28</td>
<td>1.1</td>
<td>251 (33.8)</td>
<td>3.0 (2.5)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>236 (31.8)</td>
<td>2.6 (2.3)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>0.25</td>
</tr>
<tr>
<td>BDE-47</td>
<td>2.5</td>
<td>708 (95.4)</td>
<td>21.5 (3.7)</td>
<td>16.3 (7.9-38.8)</td>
<td>707 (95.3)</td>
<td>21.0 (3.2)</td>
<td>16.9 (8.4-38.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>BDE-66</td>
<td>1.2</td>
<td>66 (8.9)</td>
<td>2.9 (2.3)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>52 (7.0)</td>
<td>2.3 (2.1)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>0.15</td>
</tr>
<tr>
<td>BDE-85</td>
<td>1.0</td>
<td>208 (28.0)</td>
<td>3.3 (3.0)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>204 (27.5)</td>
<td>2.8 (2.6)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>0.67</td>
</tr>
<tr>
<td>BDE-99</td>
<td>2.0</td>
<td>549 (74.0)</td>
<td>9.1 (3.6)</td>
<td>4.1 (&lt;LOD-10.6)</td>
<td>577 (77.8)</td>
<td>8.2 (3.2)</td>
<td>4.4 (2.2-10.6)</td>
<td>0.60</td>
</tr>
<tr>
<td>BDE-100</td>
<td>1.0</td>
<td>621 (83.7)</td>
<td>5.7 (3.5)</td>
<td>3.4 (1.5-8.8)</td>
<td>643 (86.7)</td>
<td>5.4 (3.0)</td>
<td>3.7 (1.8-8.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>BDE-153</td>
<td>1.0</td>
<td>579 (78.5)</td>
<td>6.4 (3.4)</td>
<td>4.3 (2.1-11.5)</td>
<td>579 (78.5)</td>
<td>5.4 (3.0)</td>
<td>3.7 (1.8-8.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>BDE-154</td>
<td>1.0</td>
<td>549 (74.0)</td>
<td>9.1 (3.6)</td>
<td>4.3 (&lt;LOD-10.6)</td>
<td>707 (95.3)</td>
<td>21.0 (3.2)</td>
<td>16.9 (8.4-38.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>BDE-183</td>
<td>1.1</td>
<td>79 (10.7)</td>
<td>1.7 (2.0)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>85 (11.5)</td>
<td>1.5 (1.7)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>0.68</td>
</tr>
<tr>
<td>BDE-209</td>
<td>5.2</td>
<td>544 (73.3)</td>
<td>3.0 (2.3)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>550 (74.1)</td>
<td>3.1 (2.2)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>0.14</td>
</tr>
<tr>
<td>BB-153</td>
<td>1.0</td>
<td>544 (73.3)</td>
<td>3.0 (2.3)</td>
<td>2.0 (&lt;LOD-3.5)</td>
<td>550 (74.1)</td>
<td>3.1 (2.2)</td>
<td>&lt;LOD (&lt;LOD-&lt;LOD)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Abbreviation: PBDE, polybrominated diphenyl ether; PBB, polybrominated biphenyl; PTC, papillary thyroid cancer; LOD: limit of detection; GSD, geometric standard deviation; IQR, interquartile range; 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',3,4',5'-hexabromodiphenyl ether; BDE-154, 2,2',4,4',5,6-hexabromodiphenyl ether; BDE-183, 2,2',3,4',5,6-heptabromodiphenyl ether; BDE-209, 2,2',3,3',4',4',5,5'-hexabromodiphenyl ether; BB-153, 2,2',4,4',5,5'-hexabromobiphenyl.

<sup>a</sup>Calculated among cases and controls combined.

<sup>b</sup>Estimated by the Mann-Whitney U test.
Table 2. Distributions of selected characteristics among PTC cases and matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Cases No. (%)</th>
<th>Controls No. (%)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at serum samples collection (year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>124 (16.7)</td>
<td>121 (16.3)</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>348 (46.9)</td>
<td>352 (47.4)</td>
<td></td>
</tr>
<tr>
<td>30-40</td>
<td>220 (29.7)</td>
<td>221 (29.8)</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>50 (6.7)</td>
<td>48 (6.5)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Age at diagnosis (year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>210 (28.3)</td>
<td>203 (27.4)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>310 (41.8)</td>
<td>323 (43.5)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>185 (24.9)</td>
<td>179 (24.1)</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>37 (5.0)</td>
<td>37 (5.0)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>401 (54.0)</td>
<td>401 (54.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>341 (46.0)</td>
<td>341 (46.0)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>468 (63.1)</td>
<td>467 (63.0)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>131 (17.7)</td>
<td>132 (17.8)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>68 (9.2)</td>
<td>68 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>55 (7.4)</td>
<td>55 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>20 (2.7)</td>
<td>20 (2.7)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>257 (34.6)</td>
<td>285 (38.4)</td>
<td></td>
</tr>
<tr>
<td>25-29.9</td>
<td>148 (20.0)</td>
<td>129 (17.4)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>16 (2.2)</td>
<td>10 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>321 (43.3)</td>
<td>318 (42.9)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Service</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Army</td>
<td>300 (40.4)</td>
<td>263 (35.4)</td>
<td></td>
</tr>
<tr>
<td>Air Force</td>
<td>197 (26.6)</td>
<td>152 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Marines and Coast Guard combined</td>
<td>61 (8.2)</td>
<td>83 (11.2)</td>
<td></td>
</tr>
<tr>
<td>Navy</td>
<td>184 (24.8)</td>
<td>244 (32.9)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Year of serum samples collection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-2000</td>
<td>570 (76.8)</td>
<td>571 (77.0)</td>
<td></td>
</tr>
<tr>
<td>2001-2004</td>
<td>135 (18.2)</td>
<td>133 (17.9)</td>
<td></td>
</tr>
<tr>
<td>2005-2009</td>
<td>37 (5.0)</td>
<td>38 (5.1)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Years between serum samples collection and PTC diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>115 (15.5)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>344 (46.4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10-12</td>
<td>283 (38.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Histologic subtype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical PTC</td>
<td>600 (80.9)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Follicular variation of PTC</td>
<td>142 (19.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>235 (31.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>463 (62.4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>44 (5.9)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index; PTC, papillary thyroid cancer.

*a Estimated by the Chi-squared test.*
Table 3. Risk of PTC associated with lipid-corrected serum concentrations of PBDE and PBB congeners (ng/g), stratified by histologic subtype.

<table>
<thead>
<tr>
<th></th>
<th>Classical PTC</th>
<th>Follicular variation of PTC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td><strong>BDE-28</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;LOD</td>
<td>383</td>
<td>406</td>
</tr>
<tr>
<td>&gt;LOD-1.56</td>
<td>55</td>
<td>63</td>
</tr>
<tr>
<td>1.57-3.18</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>3.19-80.10</td>
<td>87</td>
<td>61</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BDE-47</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;LOD-8.43</td>
<td>159</td>
<td>150</td>
</tr>
<tr>
<td>8.44-16.91</td>
<td>141</td>
<td>150</td>
</tr>
<tr>
<td>16.92-38.63</td>
<td>137</td>
<td>142</td>
</tr>
<tr>
<td>38.64-2189.00</td>
<td>156</td>
<td>150</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BDE-85</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;LOD</td>
<td>423</td>
<td>433</td>
</tr>
<tr>
<td>&gt;LOD-1.68</td>
<td>61</td>
<td>55</td>
</tr>
<tr>
<td>1.69-3.18</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>3.19-79.08</td>
<td>81</td>
<td>53</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BDE-99</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;LOD-2.17</td>
<td>168</td>
<td>149</td>
</tr>
<tr>
<td>2.18-4.40</td>
<td>133</td>
<td>150</td>
</tr>
<tr>
<td>4.41-10.61</td>
<td>142</td>
<td>147</td>
</tr>
<tr>
<td>10.62-993.30</td>
<td>152</td>
<td>151</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BDE-100</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;LOD-1.84</td>
<td>177</td>
<td>151</td>
</tr>
<tr>
<td>1.85-3.71</td>
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</tr>
<tr>
<td>3.72-8.65</td>
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<td>144</td>
</tr>
<tr>
<td></td>
<td>BB-153</td>
<td>BDE-153</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>8.66-368.00</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>0.67 (0.27, 1.65)</td>
<td>0.19 (0.03, 1.41)</td>
</tr>
<tr>
<td>P for trend&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.29</td>
<td>0.13</td>
</tr>
<tr>
<td>BDE-153</td>
<td></td>
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</tr>
<tr>
<td>&lt;LOD-2.49</td>
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<td>149</td>
</tr>
<tr>
<td>2.50-4.61</td>
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<td>36</td>
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<tr>
<td>4.62-11.23</td>
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<td>38</td>
</tr>
<tr>
<td>11.24-285.50</td>
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<tr>
<td>P for trend&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0.13</td>
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<tr>
<td>BDE-154</td>
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<td>&lt;LOD</td>
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<td>426</td>
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<td>57</td>
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<tr>
<td>3.12-66.22</td>
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<td>55</td>
</tr>
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<td>P for trend&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.49</td>
<td>0.76</td>
</tr>
<tr>
<td>BB-153</td>
<td></td>
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</tr>
<tr>
<td>&lt;LOD-0.85</td>
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<td>149</td>
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<td>0.86-2.12</td>
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<td>146</td>
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<td>2.13-3.60</td>
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<td>3.61-451.30</td>
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<td>142</td>
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<td>P for trend&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0.60</td>
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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; LOD: limit of detection; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PTC, papillary thyroid cancer.

<sup>a</sup> Multi-chemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m², and missing), and branch of military service (Army, Air Force, Navy, and Marines/Coast Guard).

<sup>b</sup> P-values were not corrected for multiple comparison.
Table 4. Risk of classical PTC associated with lipid-corrected serum concentrations of PBDE and PBB congeners (ng/g), stratified by tumor size.

<table>
<thead>
<tr>
<th>BDE-28</th>
<th>≤10 mm</th>
<th></th>
<th>≥10 mm</th>
<th></th>
</tr>
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<td>215</td>
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<td>22</td>
<td>40</td>
<td>39</td>
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<tr>
<td>1.57-3.18</td>
<td>22</td>
<td>22</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>3.19-80.10</td>
<td>25</td>
<td>30</td>
<td>58</td>
<td>31</td>
</tr>
<tr>
<td>P for trend b</td>
<td>0.57</td>
<td></td>
<td>0.0014</td>
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</tr>
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<td>BDE-47</td>
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<td></td>
<td></td>
</tr>
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<td>91</td>
</tr>
<tr>
<td>8.44-16.91</td>
<td>44</td>
<td>47</td>
<td>84</td>
<td>92</td>
</tr>
<tr>
<td>16.92-38.63</td>
<td>44</td>
<td>50</td>
<td>87</td>
<td>81</td>
</tr>
<tr>
<td>38.64-2189.00</td>
<td>52</td>
<td>54</td>
<td>96</td>
<td>92</td>
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<tr>
<td>P for trend b</td>
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<td>0.75</td>
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<td>BDE-85</td>
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<td>258</td>
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</tr>
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<td>1.69-3.18</td>
<td>7</td>
<td>14</td>
<td>22</td>
<td>41</td>
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<tr>
<td>3.19-79.08</td>
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<td>53</td>
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<td>P for trend b</td>
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<td>BDE-99</td>
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<td>94</td>
<td>87</td>
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<tr>
<td>2.18-4.40</td>
<td>44</td>
<td>47</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>4.41-10.61</td>
<td>46</td>
<td>49</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>10.62-993.30</td>
<td>49</td>
<td>56</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>P for trend b</td>
<td>0.92</td>
<td></td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>BDE-100</td>
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<td>49</td>
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<td>1.85-3.71</td>
<td>43</td>
<td>48</td>
<td>82</td>
<td>95</td>
</tr>
<tr>
<td>3.72-8.65</td>
<td>43</td>
<td>49</td>
<td>70</td>
<td>82</td>
</tr>
</tbody>
</table>

- BDE: Brominated diphenyl ether
- PBB: Polybrominated biphenyl
- OR: Odds Ratio
- CI: Confidence Interval
- LOD: Limit of Detection
<table>
<thead>
<tr>
<th>Concentration Range</th>
<th>Sample Size</th>
<th>OR (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.66-368.00</td>
<td>47</td>
<td>0.26 (0.05, 1.32)</td>
<td>0.094</td>
</tr>
<tr>
<td>2.50-4.61</td>
<td>76</td>
<td>0.76 (0.40, 1.44)</td>
<td>0.94 (0.58, 1.53)</td>
</tr>
<tr>
<td>4.62-11.23</td>
<td>81</td>
<td>0.80 (0.37, 1.76)</td>
<td>0.84 (0.47, 1.50)</td>
</tr>
<tr>
<td>11.24-285.50</td>
<td>103</td>
<td>2.74 (0.96, 7.86)</td>
<td>0.66 (0.33, 1.32)</td>
</tr>
<tr>
<td>BDE-153</td>
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<td>0.72</td>
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<tr>
<td>&lt;LOD-2.49</td>
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<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2.50-4.61</td>
<td>76</td>
<td>0.76 (0.40, 1.44)</td>
<td>0.94 (0.58, 1.53)</td>
</tr>
<tr>
<td>4.62-11.23</td>
<td>81</td>
<td>0.80 (0.37, 1.76)</td>
<td>0.84 (0.47, 1.50)</td>
</tr>
<tr>
<td>11.24-285.50</td>
<td>103</td>
<td>2.74 (0.96, 7.86)</td>
<td>0.66 (0.33, 1.32)</td>
</tr>
<tr>
<td>BDE-154</td>
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<td>1.00</td>
</tr>
<tr>
<td>&gt;LOD-1.60</td>
<td>44</td>
<td>0.35 (0.11, 1.14)</td>
<td>3.33 (1.50, 7.36)</td>
</tr>
<tr>
<td>1.61-3.11</td>
<td>37</td>
<td>0.15 (0.02, 0.93)</td>
<td>3.40 (1.18, 9.85)</td>
</tr>
<tr>
<td>3.12-6.66</td>
<td>45</td>
<td>0.04 (0.003, 0.51)</td>
<td>1.74 (0.39, 7.80)</td>
</tr>
<tr>
<td>BB-153</td>
<td></td>
<td></td>
<td>0.039</td>
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<tr>
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<td>1.00</td>
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<tr>
<td>0.86-2.12</td>
<td>88</td>
<td>1.02 (0.55, 1.90)</td>
<td>0.81 (0.51, 1.28)</td>
</tr>
<tr>
<td>2.13-3.60</td>
<td>90</td>
<td>0.86 (0.46, 1.62)</td>
<td>0.74 (0.47, 1.18)</td>
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<tr>
<td>3.61-451.30</td>
<td>86</td>
<td>0.87 (0.45, 1.67)</td>
<td>0.85 (0.54, 1.36)</td>
</tr>
</tbody>
</table>

Abbreviation: BB-153, 2,2',4,4',5,5'-hexabromodiphenyl ether; 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',5,6'-hexabromodiphenyl ether; BDE-154, 2,2',4,4',5,6'-hexabromodiphenyl ether; BMI, body mass index; LOD: limit of detection; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PTC, papillary thyroid cancer.

aMulti-chemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m², and missing), and branch of military service (Army, Air Force, Navy, and Marines/Coast Guard).

bP-values were not corrected for multiple comparison.
Table 5. Risk of large classical PTC (>10 mm) associated with lipid-corrected serum concentrations of PBDE and PBB congeners (ng/g), stratified by gender.

<table>
<thead>
<tr>
<th>BDE</th>
<th>Male Cases</th>
<th>Controls</th>
<th>ORa (95% CI)</th>
<th>Female Cases</th>
<th>Controls</th>
<th>ORa (95% CI)</th>
<th>P for interactionb</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<td>1.00</td>
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<td>111</td>
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<tr>
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<td>21</td>
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<td>15</td>
<td>18</td>
<td>1.13 (0.39, 3.30)</td>
<td>0.0040</td>
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<tr>
<td>1.57-3.18</td>
<td>26</td>
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<td>17</td>
<td>12</td>
<td>3.56 (0.87, 14.63)</td>
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</tr>
<tr>
<td>3.19-80.10</td>
<td>26</td>
<td>20</td>
<td>3.39 (0.98, 11.71)</td>
<td>32</td>
<td>11</td>
<td>10.74 (1.93, 59.72)</td>
<td></td>
</tr>
<tr>
<td>P for trendb</td>
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<td>1.00</td>
<td>37</td>
<td>41</td>
<td>1.00</td>
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</tr>
<tr>
<td>8.44-16.91</td>
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<td>46</td>
<td>1.26 (0.56, 2.82)</td>
<td>32</td>
<td>46</td>
<td>1.43 (0.57, 3.59)</td>
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</tr>
<tr>
<td>16.92-38.63</td>
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<td>54</td>
<td>0.94 (0.31, 2.87)</td>
<td>31</td>
<td>27</td>
<td>3.08 (0.79, 12.02)</td>
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<tr>
<td>38.64-2189.00</td>
<td>46</td>
<td>54</td>
<td>0.41 (0.08, 2.12)</td>
<td>50</td>
<td>38</td>
<td>0.67 (0.07, 6.09)</td>
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</tr>
<tr>
<td>P for trendb</td>
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<td></td>
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<tr>
<td>BDE-85</td>
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<td>&gt;LOD-1.68</td>
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<td>23</td>
<td>0.56 (0.21, 1.45)</td>
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<td>1.03 (0.17, 6.40)</td>
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<tr>
<td>1.69-3.18</td>
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<td>20</td>
<td>0.17 (0.02, 1.49)</td>
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</tr>
<tr>
<td>3.19-79.08</td>
<td>22</td>
<td>19</td>
<td>0.40 (0.07, 2.52)</td>
<td>31</td>
<td>10</td>
<td>2.46 (0.12, 51.74)</td>
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<tr>
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<td>2.18-4.40</td>
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<td>0.89 (0.39, 2.03)</td>
<td>31</td>
<td>42</td>
<td>0.72 (0.29, 1.81)</td>
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<tr>
<td>4.41-10.61</td>
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<td>52</td>
<td>1.02 (0.34, 3.02)</td>
<td>34</td>
<td>36</td>
<td>0.48 (0.14, 1.61)</td>
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</tr>
<tr>
<td>10.62-993.30</td>
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<td>56</td>
<td>1.00 (0.24, 4.25)</td>
<td>47</td>
<td>35</td>
<td>0.51 (0.09, 2.85)</td>
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</tr>
<tr>
<td>P for trendb</td>
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<td>1.00</td>
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</tr>
<tr>
<td>1.85-3.71</td>
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<td>48</td>
<td>0.74 (0.31, 1.77)</td>
<td>33</td>
<td>47</td>
<td>0.58 (0.21, 1.56)</td>
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</tr>
</tbody>
</table>
### BDE-153

<table>
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<th>50</th>
<th>54</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.50-4.61</td>
<td>45</td>
<td>49</td>
<td>0.78 (0.40, 1.54)</td>
<td>31</td>
<td>37</td>
<td>0.95 (0.44, 2.07)</td>
</tr>
<tr>
<td>4.62-11.23</td>
<td>51</td>
<td>55</td>
<td>0.82 (0.38, 1.76)</td>
<td>30</td>
<td>32</td>
<td>0.70 (0.25, 1.96)</td>
</tr>
<tr>
<td>11.24-285.50</td>
<td>62</td>
<td>69</td>
<td>0.59 (0.23, 1.55)</td>
<td>41</td>
<td>30</td>
<td>0.59 (0.18, 1.91)</td>
</tr>
</tbody>
</table>

*P for trend*\(^b\) 0.39 0.50 0.077

### BDE-154

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<tr>
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<th>117</th>
<th>1.00</th>
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</thead>
<tbody>
<tr>
<td>&gt;LOD-1.60</td>
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<td>22</td>
<td>2.57 (0.98, 6.73)</td>
<td>16</td>
<td>9</td>
<td>4.43 (0.94, 20.80)</td>
</tr>
<tr>
<td>1.61-3.11</td>
<td>18</td>
<td>24</td>
<td>2.59 (0.69, 9.64)</td>
<td>19</td>
<td>14</td>
<td>4.65 (0.56, 38.40)</td>
</tr>
<tr>
<td>3.12-66.22</td>
<td>21</td>
<td>17</td>
<td>3.45 (0.52, 22.96)</td>
<td>24</td>
<td>12</td>
<td>0.54 (0.02, 13.54)</td>
</tr>
</tbody>
</table>

*P for trend*\(^b\) 0.061 0.40 0.0070

### BB-153

<table>
<thead>
<tr>
<th>&lt;LOD-0.85</th>
<th>41</th>
<th>34</th>
<th>1.00</th>
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<th>58</th>
<th>1.00</th>
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</thead>
<tbody>
<tr>
<td>0.86-2.12</td>
<td>41</td>
<td>41</td>
<td>0.66 (0.32, 1.35)</td>
<td>47</td>
<td>43</td>
<td>0.84 (0.44, 1.63)</td>
</tr>
<tr>
<td>2.13-3.60</td>
<td>61</td>
<td>63</td>
<td>0.67 (0.35, 1.27)</td>
<td>29</td>
<td>32</td>
<td>0.83 (0.40, 1.75)</td>
</tr>
<tr>
<td>3.61-451.30</td>
<td>63</td>
<td>66</td>
<td>0.70 (0.37, 1.34)</td>
<td>23</td>
<td>19</td>
<td>0.99 (0.42, 2.32)</td>
</tr>
</tbody>
</table>

*P for trend*\(^b\) 0.46 0.92 0.16

### 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; LOD: limit of detection; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PTC, papillary thyroid cancer.

\(^a\) Multi-chemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m\(^2\), and missing), and branch of military service (Army, Air Force, Navy, and Marines/Coast Guard).

\(^b\) P-values were not corrected for multiple comparison.
Supplementary Table 1. Geometric means and GSDs of lipid-corrected serum concentrations of selected PBDE and PBB congeners (ng/g) among PTC cases by demographic characteristics and military services.

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Abbreviation: GSD, geometric standard deviation; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; PTC, papillary thyroid cancer; 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; BB-153, 2,2',4,4',5,5'-hexabromobiphenyl; BMI, body mass index.
Supplementary Table 2. Geometric means and GSDs of lipid-corrected serum concentrations of selected PBDE and PBB congeners (ng/g) among controls by demographic characteristics and military services.

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Abbreviation: GSD, geometric standard deviation; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; PTC, papillary thyroid cancer; 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; BB-153, 2,2',4,4',5,5'-hexabromobiphenyl; BMI, body mass index.
Supplementary Table 3. Cramer’s Vs between categorical PBDE and PBB congeners detected in >20% of controls.

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Abbreviation: PBDE, polybrominated diphenyl ether; PBB, polybrominated biphenyl; 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; BB-153, 2,2’,4,4’,5,5’-hexabromobiphenyl.
Supplementary Table 4. Risk of classical PTC microcarcinoma (≤10 mm) associated with lipid-corrected serum concentrations of PBDE and PBB congeners (ng/g), stratified by gender.

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<td>0.033</td>
<td>0.92</td>
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</table>

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; LOD: limit of detection; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PTC, papillary thyroid cancer.

* Multi-chemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m², and missing), and branch of military service (Army, Air Force, Navy, and Marines/Coast Guard).

* P-values were not corrected for multiple comparison.
Supplementary Table 5. Risk of PTC associated with lipid-corrected serum concentrations of PBDE and PBB congeners (ng/g) among participants with serum samples drawn ≥5 years before PTC diagnosis, stratified by histologic subtype.

<table>
<thead>
<tr>
<th>BDE-28</th>
<th>Classical PTC</th>
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<th>Follicular variation of PTC</th>
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<td>Controls</td>
<td>OR* (95% CI)</td>
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<td>331</td>
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<tr>
<td>&gt;LOD-1.56</td>
<td>47</td>
<td>55</td>
<td>1.03 (0.62, 1.70)</td>
<td>14</td>
</tr>
<tr>
<td>1.57-3.18</td>
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<td>52</td>
<td>1.80 (1.00, 3.21)</td>
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</tr>
<tr>
<td>3.19-80.10</td>
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<td>55</td>
<td>2.53 (1.19, 5.36)</td>
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<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
<td>Cases</td>
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<td>8.44-16.91</td>
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<td>16.92-38.63</td>
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<td>130</td>
<td>1.09 (0.41, 2.90)</td>
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<td>Controls</td>
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<tr>
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<td>1.69-3.18</td>
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<tr>
<td>3.19-79.08</td>
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<td>2.11 (0.60, 7.40)</td>
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<td>P for trend</td>
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<td>2.18-4.40</td>
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<tr>
<td>4.41-10.61</td>
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<td>0.80 (0.42, 1.52)</td>
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<td>10.62-993.30</td>
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<td>132</td>
<td>0.79 (0.33, 1.87)</td>
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<td>P for trend</td>
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<td>1.85-3.71</td>
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<td>118</td>
<td>0.72 (0.43, 1.23)</td>
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<td>Controls</td>
<td>OR</td>
<td>95% CI</td>
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<td>---------------</td>
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<tr>
<td>3.72-8.65</td>
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<td>126</td>
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<tr>
<td>8.66-368.00</td>
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<td>(0.19, 1.40)</td>
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<tr>
<td><strong>P for trend</strong></td>
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**BDE-153**

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<th>Controls</th>
<th>OR</th>
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<td>118</td>
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<td>33</td>
<td>1.00</td>
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<tr>
<td>2.50-4.61</td>
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<td>(0.78, 4.75)</td>
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<td>1.78</td>
<td>(0.62, 5.06)</td>
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<td>11.24-285.50</td>
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**BDE-154**

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<td>81</td>
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<td>&gt;LOD-1.60</td>
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<td>(0.68, 2.47)</td>
<td>12</td>
<td>12</td>
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<td>(0.21, 3.19)</td>
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<td>6</td>
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<td>(0.05, 2.67)</td>
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<td>3.12-66.22</td>
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<td>11</td>
<td>0.76</td>
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**BB-153**

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<td>0.92</td>
<td>(0.39, 2.19)</td>
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<tr>
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<td>0.72</td>
<td>(0.49, 1.05)</td>
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<td>24</td>
<td>1.35</td>
<td>(0.56, 3.26)</td>
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<tr>
<td>3.61-451.30</td>
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<td>121</td>
<td>0.80</td>
<td>(0.54, 1.18)</td>
<td>28</td>
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<td>0.80</td>
<td>(0.33, 1.94)</td>
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Abbreviation: PTC, papillary thyroid cancer; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; OR, odds ratio; 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; BB-153, 2,2',4,4',5,5'-hexabromobiphenyl; LOD: limit of detection; BMI, body mass index.

* Multi-chemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m2, and missing), and branch of military service (Army, Air Force, Navy, and Marines/Coast Guard).
### Supplementary Table 6. Statistical significance of associations between seven principal components of PBDEs and risk of classical PTC.

<table>
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<tr>
<th>Congeners</th>
<th>Principal components (% variance explained)</th>
<th>Eigenvectors</th>
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</thead>
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<tr>
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<td>#1 (87.2%)</td>
<td>#2 (8.7%)</td>
</tr>
<tr>
<td>PBDE-28</td>
<td>0.3785</td>
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<tr>
<td>PBDE-47</td>
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<td>-0.1760</td>
</tr>
<tr>
<td>PBDE-85</td>
<td>0.3968</td>
<td>-0.1771</td>
</tr>
<tr>
<td>PBDE-99</td>
<td>0.3829</td>
<td>-0.3018</td>
</tr>
<tr>
<td>PBDE-100</td>
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Test of association with risk of classical PTC

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Abbreviation: PTC, papillary thyroid cancer; PBED, polybrominated diphenyl ether; OR, odds ratio; 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; BB-153, 2,2',4,4',5,5'-hexabromobiphenyl; BMI, body mass index.

* Conditional logistic regression model including seven principal components of PBDEs, BB-153, BMI, and branch of military service.
Supplementary Figure 1. Ridge trace of association between using elastic net penalty of pure Lasso (A) and pure ridge (B).
Thyroid-Stimulating Hormone, Thyroid Hormones, and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study

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³Yale School of Public Health, New Haven, CT
⁴Cancer Institute & Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China
⁵Epidemiology Program, University of Hawaii Cancer Center, Hawaii
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⁷Endocrine Neoplasia Institute, Miami Cancer Center, Miami, FL

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Abstract

Background: The effects of thyroid-stimulating hormone (TSH) and thyroid hormones on the development of human papillary thyroid cancer (PTC) remain poorly understood.

Methods: The study population consisted of 741 (341 women, 300 men) histologically confirmed PTC cases and 741 matched controls with pre-diagnostic serum samples stored in the Department of Defense Serum Repository. Concentrations of TSH, total T3 (TT3), total T4 (TT4), and free T4 (FT4) were measured in serum samples. Conditional logistic regression models were used to calculate ORs and 95% CIs.

Results: The median time between blood draw and PTC diagnosis was 1,454 days. Compared to the middle tertile of TSH levels within the normal range, serum TSH levels below the normal range were associated with an elevated risk of PTC among women (OR=3.74, 95% CI: 1.53, 9.19) but not men. TSH levels above the normal range were associated with an increased risk of PTC among men (OR=1.96, 95% CI: 1.04, 3.66) but not women. The risk of PTC decreased with increasing TSH levels within the normal range among both men and women (P_trend=0.0005 and 0.041, respectively).

Conclusions: We found a significantly increased risk of PTC associated with TSH levels below the normal range among women and with TSH levels above the normal range among men. An inverse association between PTC and TSH levels within the normal range was observed among both men and women. These results could have significant clinical implications for physicians who are managing patients with abnormal thyroid functions and those with thyroidectomy.

Keywords: thyroid-stimulating hormone, TSH, thyroid hormone, papillary thyroid cancer
Thyroid cancer has the highest prevalence of all endocrine malignancies, and its incidence is rising faster than any other malignancy in both men and women [71]. In the United States, thyroid cancer is the 9th most common cancer, accounting for 3.8% of all malignancies and 0.3% of all deaths from cancer [72]. The most common histological type of thyroid cancer is papillary thyroid cancer (PTC), which accounts for more than 80% of all thyroid carcinomas [73]. The causal factors underlying thyroid cancer are poorly understood. The most well-established risk factors for thyroid cancer include increased age, female gender, exposure to ionizing radiation, history of benign thyroid disease, and a family history of thyroid cancer [10, 11, 13, 74]. Recent studies have identified higher body weight and height as risk factors for thyroid cancer [14, 15].

Thyroid-stimulating hormone (TSH) is the major growth factor for thyroid cells and regulator of thyroid functions. It controls the processes that lead to increased thyroid hormone production and secretion [39]. Blood concentrations of thyroid hormones (i.e., triiodothyronine [T3] and its prohormone thyroxine [T4]) inversely regulate the release of TSH through a negative feedback loop at the pituitary levels. High TSH levels have been associated with PTC pathogenesis in a mouse model [75]. Suppression of TSH is currently recommended to manage differentiated thyroid cancer (DTC) patients, which has shown benefits to patient survival [76]. Thyroid hormones have also been suggested to have a tumor promoting effect on several cancers, including pancreatic, breast, ovarian, and prostate cancer [77]. However, findings of epidemiological studies linking TSH and thyroid hormones to the risk of thyroid cancer have been inconsistent [41, 42, 68, 78-101].

The majority of early studies reported an increased risk of thyroid cancer associated with elevated TSH levels [41, 42, 78-92], several studies found no significant association [93-101], and one reported a reduced risk [68]. All studies that reported a positive association between TSH and thyroid cancer were cross-sectional [41, 42, 78-91] or case-control studies [92]. Therefore, the possibility of reverse causation or treatment effect could be of potential concern because the TSH
levels were measured after diagnosis. There are only three previous prospective cohort studies. One reported a significantly reduced risk of thyroid cancer associated with elevated TSH levels [68]. Two smaller studies reported lower, but not significant TSH levels in thyroid cancer cases than in controls [100, 101]. The relationship between thyroid hormones and risk of thyroid cancer has also been inconclusive [41, 42, 68, 78, 79, 99, 100]. Two studies found lower thyroid hormone levels were associated with a higher risk of thyroid cancer [41, 42], while the remaining five reported no association [68, 78, 79, 99, 100].

In light of the inconclusive associations between TSH, thyroid hormones, and thyroid cancer, we conducted a nested case-control study using data from the Department of Defense (DoD) Automated Central Tumor Registry (ACTUR) and the Defense Medical Surveillance System (DMSS), with pre-diagnostic serum samples from the Department of Defense Serum Repository (DoDSR) to investigate the associations of PTC with TSH and thyroid hormones (total T3 [TT3], total T4 [TT4], and free T4 [FT4]).

**Methods**

*Study population*

Our study population was US military personnel who had serum samples stored in the DoDSR [102]. These stored samples were leftover sera collected for the routine HIV test of military personnel. The DoDSR is maintained by the Armed Forces Health Surveillance Center, US Army Public Health Command. As of August 2013, the repository stored more than 55 million serum samples from over 10 million individuals, most of whom were active-duty and reserve personnel. Serum samples on all military members were typically drawn at the time of service entry and, on average, every 2 years thereafter for mandatory HIV testing [103, 104].
We designed an individually matched nested case-control study. Cases were identified by linkage of the ACTUR with the DoDSR database. The ACTUR was established in 1986 and is the data collection and clinical tracking system for cancer cases diagnosed and treated at military treatment facilities among DoD beneficiaries, including active-duty military personnel, retired military personnel, and their dependents. The registry includes information on demographic variables, diagnostic factors, and tumor characteristics [105]. Cases met the following criteria: 1) histologically confirmed with International Classification of Diseases for Oncology, third edition (ICD-O-3 for thyroid gland: C739) histology codes 8021, 8050, 8130, 8260, 8290, 8330-8332, 8335, 8340-8346, 8450, 8452, and 8510; 2) at least 1.5ml pre-diagnostic and 0.5ml post-diagnostic serum samples stored in the DoDSR; 3) diagnosis between 2000 and 2013; and 4) aged 21 years or older at diagnosis. Cases with any prior cancers (excluding non-melanoma skin cancer) recorded in the ACTUR at the date of diagnosis of thyroid cancer were excluded from the study. A total of 800 eligible cases were identified. The histology of all reported thyroid cancer cases was abstracted from ACTUR. Of these eligible cases, 742 (92.8%) were PTC (ICD-O-3: 8050, 8260, and 8340-8343). IDs for all cases were sent from ACTUR to Armed Forces Health Surveillance Center via encrypted methods. Those IDs were excluded from the eligible pool of controls. Controls’ eligibility criteria were: having at least four serum samples in DoDSR, and according to the matching criteria, the midpoint of those four samples within one year of the control’s matched case’s midpoint of their four samples. Controls were randomly selected with replacement from the cohort of service members who were not diagnosed with any cancer (with the exception of non-melanoma skin cancer), as per query of the ACTUR. Controls were matched one-to-one to cases by date of birth (±1 year), gender, race/ethnicity (White, Black, Hispanic, and other), average date of the selected four samples drawn (±1 year), and component at diagnosis/matching. Demographic and military characteristics for all cases and controls were abstracted from DMSS. The DMSS now serves as the central repository of medical surveillance data for the US armed forces and contains longitudinal records which have been continuously updated since 1990. The system includes
demographic and military characteristics as well as military and medical experiences of service members throughout their military careers [102]. All study procedures were approved by the Uniformed Services University Institutional Review Board, the Walter Reed National Military Medical Center, the DoD Joint Pathology Center, and The Human Investigation Committee of Yale University.

**Measurement of TSH and thyroid hormones**

A calibrated Roche Cobas e601 analyzer was used to measure the serum concentrations of TSH and thyroid hormones using the manufacturer’s reagents and calibrators. TSH was captured between two monoclonal antibodies (one was biotinylated, the other labeled with a ruthenium complex) which specific for sterically non-interfering epitopes of human TSH. TT3 and TT4 were dissociated from binding proteins using 8-anilino-1-naphthalene sulfonic acid (ANS) and competed with the exogenous biotinylated-T3 or -T4 for binding to a T3- or T4-specific antibody labeled with a ruthenium complex. FT4 directly competed with the exogenous biotinylated-T4 for binding to a T4-specific antibody labeled with a ruthenium complex. All the antibodies were captured by streptavidin-coated magnetic microparticles, which were then magnetically captured by an electrode and the application of voltage induced emission of photons by the ruthenium complex. The intensities of the luminescence were inversely proportional to the serum concentrations of TSH and thyroid hormones. The normal ranges for serum concentrations of TSH, TT3, TT4, and FT4 were 0.3-4.2 μU/ml, 79-149 ng/dl, 5.0-10.6 μg/dl, and 0.80-1.80 ng/dl, respectively. All control samples were tested in the same batch as their matched case samples. Based on results obtained from quality-control samples (5%), intra-batch coefficient of variation ranged from 3.9% to 7.7%.

**Statistical analyses**

Measurements of TSH and thyroid hormones failed in one serum sample, leaving 741 pairs of PTC cases and matched controls included in the final analysis. The distributions of demographic and
military characteristics between cases and controls were compared by chi-square tests. The correlations between TSH, TT3, TT4, and FT4 were estimated using the Pearson correlation coefficients. Given the individual-matched case-control design, conditional logistic regression analyses were employed to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between TSH, thyroid hormones and PTC. Serum concentrations of TSH, TT3, TT4, and FT4 were divided into three categories based on the normal range (below, within, and above the normal range). The normal range group was further categorized into tertiles based on the distributions of serum concentrations among controls. Thus, there were five categories for each hormone: below the normal range, lower, medium, and higher levels within the normal range, and above the normal range. The middle tertile within the normal range was used as reference category for all analyses. All the conditional logistic regression models were adjusted for body mass index (BMI) (<18.5, 18.5-24.9, 25-29.9, and ≥30 kg/m²) and branch of military service (army, air force, marines and coast guard, and navy). TT3, TT4, and FT4 models were also adjusted for serum concentrations of TSH. However, additional adjustment for serum concentrations of TT3, TT4, and FT4 in TSH models did not result in material changes in the observed associations and thus were not included in the final models. Dose-response relationship was further investigated using P for trend, estimated by treating serum concentrations of TSH and thyroid hormones as continuous variables. Stratified analyses were performed by gender, histological subtype (classical PTC [ICD-O-3: 8050, 8260, 8341-8343] and follicular variant of PTC [ICD-O-3: 8340]), tumor size (≤10 and >10 mm), and years between serum samples drawn and PTC diagnosis (<3 years, 3-6 years, and >6 years, based on sample size). Sensitivity analysis was also conducted among women aged <50 years old to see if estrogen impacts the associations among premenopausal women. All tests were two-sided with α=0.05. Statistical analyses were conducted using SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results
PTC cases were more likely to have served in the Army or Air Force at time of diagnosis, while controls were more likely to have served in the Navy, Marines, or Coast Guard (Table 1). Cases had a slightly larger BMI compared to controls, but the difference was not statistically significant. Since the cases were individually matched to controls based on age, gender, and race/ethnicity, the distributions of these variables were similar between cases and controls.

All serum samples were drawn between 83 and 4,232 days before the cases were diagnosed with PTC. As anticipated, there were statistically significant strong positive correlations between TT3, TT4, and FT4 (r=0.68 for TT3 and TT4, p<0.0001; r=0.40 for TT3 and FT4, p<0.0001; and r=0.52 for TT4 and FT4, p<0.0001, respectively). TSH was weakly, but statistically significantly correlated with TT3, TT4, and FT4 (r=−0.06 for TSH and TT3, p=0.022; r=−0.17 for TSH and TT4, p<0.0001; and r=−0.19 for TSH and FT4, p<0.0001, respectively). Female cases had lower mean TSH levels as compared to their matched controls, while male cases had higher mean TSH levels as compared to their matched controls. None of these differences were statistically significant. We also observed non-significantly higher mean levels of thyroid hormones among female cases as compared to female controls, but thyroid hormone levels were similar between cases and controls among men.

In the overall population, serum TSH levels below the normal range were associated with a significantly increased risk of PTC (OR=2.65, 95% CI: 1.27, 5.52, Figure 1) compared to the middle tertile of the normal range. Paradoxically, TSH levels above the normal range were also associated with an increased risk of PTC (OR=1.58, 95% CI: 0.97, 2.56) with borderline significance. Serum concentrations of TT3, TT4, and FT4 below or above the normal range were not significantly related to an elevated risk of PTC. Within the normal ranges, the risk of PTC decreased with increasing TSH levels (P\text{trend}=0.0001) and with decreasing TT3 levels (P\text{trend}=0.031), but no dose-response relationships were observed for TT4 and FT4.
TSH levels below the normal range were associated with increased risk of PTC among women (OR=3.74, 95% CI: 1.53, 9.19) but not among men (OR=1.07, 95% CI: 0.25, 4.62, Figure 2) compared to the middle tertile of the normal range. Additionally, an increased risk of PTC in relation to TSH levels above the normal range was observed only among men (OR=1.96, 95% CI: 1.04, 3.66) but not among women (OR=1.09, 95% CI: 0.49, 2.46). The risk of PTC decreased with increasing TSH levels within the normal range among both men and women (P\text{trend}=0.0005 and 0.041, respectively). However, lower TSH levels within the normal range were associated with an increased risk of PTC and the association was stronger in women (OR=1.53, 95% CI: 1.03, 2.28) than in men (OR=1.17, 95% CI: 0.80, 1.71). In contrast, higher TSH levels within the normal range were associated with a reduced risk of PTC among men (OR=0.65, 95% CI: 0.44, 0.95). An inverse association between TT3 levels above the normal range and risk of PTC was observed only among men (OR=0.59, 95% CI: 0.36, 0.98); while the risk of PTC increased with increasing serum concentrations of TT3 among women (overall P\text{trend}=0.019). No significant associations with TT4 and FT4 were observed.

When the analyses were stratified by histological subtype among men (Figure 3), TSH levels above the normal range were borderline significantly associated with an increased risk of classical PTC (OR=1.94, 95% CI: 1.00, 3.77). A significantly inverse dose-response relationship was observed between TSH levels within the normal range and risk of classical PTC (P\text{trend}=0.0010) but not follicular variant PTC (P\text{trend}=0.16). TT3 levels above the normal range were significantly associated with a decreased risk of classical PTC (OR=0.53, 95% CI: 0.30, 0.94). When the analyses were stratified by histological subtype among women (Figure 4), TSH levels below the normal range were associated with a significantly increased risk of classical PTC (OR=2.72, 95% CI: 1.09, 6.78). The lower TSH levels within the normal range were associated with an elevated risk of follicular variant of PTC (OR=11.31, 95% CI: 3.10, 41.31). There was an increasing trend
in risk of classical PTC with increasing TT3 levels ($P_{\text{trend}}=0.021$), but no statistically significant association between TT3 levels and risk of follicular variant of PTC was observed.

When the analyses were stratified by tumor size among men (Figure 5), the higher TSH levels within the normal range were associated with a reduced risk of PTC with tumor size greater than 10 mm (OR=0.57, 95% CI: 0.35, 0.92) but not PTC microcarcinoma ($\leq 10$ mm) (OR=0.99, 95% CI: 0.47, 2.12). TSH levels within the normal range were inversely associated with PTC >10 mm ($P_{\text{trend}}=0.0003$), whereas, there was no trend for PTC microcarcinoma ($P_{\text{trend}}=0.21$). When the analyses were stratified by tumor size among women (Figure 6), TSH levels below the normal range were associated with a significantly increased risk of PTC >10 mm (OR=4.98, 95% CI: 1.30, 19.06) and a non-significantly elevated risk of PTC microcarcinoma (OR=3.62, 95% CI: 0.85, 15.48). The lower TSH levels within the normal range were associated with an elevated risk of PTC microcarcinoma (OR=2.47, 95% CI: 1.10, 5.55) but not PTC >10 mm (OR=1.30, 95% CI: 0.79, 2.14). TSH levels within the normal range were inversely associated with PTC >10 mm ($P_{\text{trend}}=0.027$). No significant associations were found for TT3, TT4, and FT4 for both PTC microcarcinoma and PTC >10 mm among men and women.

Further stratified analyses were conducted by the years between serum samples drawn and PTC diagnosis (Supplementary Table 1). No clear pattern was observed with timing of the serum samples drawn, though numbers of cases were small after stratification.

Sensitivity analyses showed that the associations between risk of PTC and serum concentrations of TSH, TT3, TT4, and FT4 did not change materially after restricting the analyses to women aged <50 years old.

Discussion
In this large case-control study based on pre-diagnostic serum measures and with sufficient power to stratify by gender, we found that serum TSH levels below the normal range were associated with an elevated risk of PTC among women but not men. TSH levels above the normal range were only associated with an increased risk of PTC among men. There was an inverse association between PTC and TSH levels within the normal range among both men and women. The observed associations varied somewhat by histological subtypes (classical vs. follicular variant PTCs) and by tumor size (≤10mm vs. >10mm) among men and women. The gender effect on the association between TSH and PTC was only observed among classical PTC cases. TSH levels showed a stronger association with PTC with larger tumor size. A suggestive inverse association between higher TT3 levels and risk of PTC was observed among men.

The inverse trends between TSH levels and risk of PTC observed in the present study was in accordance with results from a nested case-control study within a large population-based prospective cohort in Europe [68]. The cohort consisted of approximately 520,000 healthy individuals aged 35 to 69 years when recruited between 1992 and 1998 in 10 European countries. A total of 357 incident thyroid cancer cases (57 men and 300 women) diagnosed during 1992 to 2009 and 767 matched controls were included in the analyses. Blood samples were collected at enrollment. This European study found an inverse dose-response relationship between overall TSH levels and risk of differentiated thyroid cancer. The years between sample collection and thyroid cancer diagnosis were similar between the European study and our study. However, as compared to the European study, our population was younger and healthier [106], with participants aged 17 to 56 years at blood samples collection. Additionally, our study had a larger number of the male cases than the European study, which provides sufficient power to examine the associations among men. The present study observed inconsistent associations between TSH levels and risk of PTC among women as compared to men, while the European study reported similar associations among men and women. There were another two prospective studies with smaller sample size that
investigated the association between TSH and risk of thyroid cancer [100, 101]. Although no significantly inverse association was observed in these studies, both reported lower TSH levels among thyroid cancer cases as compared to controls.

A previous meta-analysis showed that higher TSH levels were associated with an increased thyroid cancer risk [107]. However, all 22 studies included in the meta-analysis were cross-sectional studies and measured TSH levels after treatment of thyroid cancer began. The cross-sectional design could not clarify whether elevated TSH levels preceded thyroid cancer diagnosis or were effects of treatment. The low levels of thyroid hormones due to dysfunction of the thyroid gland among thyroid cancer patients could cause the pituitary gland to release more TSH. Additionally, higher TSH levels may promote the growth of already initiated thyroid cancer, making the cancer larger and more easily diagnosed. Therefore, the positive association seen in the cross-sectional studies could be due to ascertainment bias [39]. On the other hand, controls in these studies were always patients with thyroid nodules or patients undergoing surgical treatment for a suspicious thyroid tumor. Some nodules can produce high levels of thyroid hormones, thus lowering TSH levels [68]. Many thyroid cancer patients also had additional benign thyroid nodules, and the mutual influence between those nodules and TSH concentrations has not yet been determined [80].

TSH plays an important role in regulating thyroid function, including increasing number, size, and secretory activity of thyrocytes, increasing thyroid blood flow, and increasing thyroid hormone production and secretion from follicular thyroid cells [39]. Classical TSH actions are mainly mediated through the $G_{\alpha s}$-adenylyl cyclase-protein kinase A-cyclic adenosine monophosphate (cAMP) pathway, which is associated with production of thyroid hormones and proliferation of thyroid epithelial cells [108]. However, somatic mutations in thyroid epithelial cell can also activate the cAMP pathway, which facilitate the cell growth and clonal expansion, leading to the formation of an autonomously functioning thyroid adenoma. The adenoma can synthesize and secrete thyroid
hormones autonomously, thereby suppressing TSH secretion [109]. Therefore, constitutive activation of the cAMP pathway could be associated with an increased carcinogenic potential and a decreased TSH level. Due to the deprivation of TSH stimulation, the extra-nodular tissue would become quiescent. Depending on the iodine intake, growth potential, and other factors, it may take months to a decade or longer for an adenoma to grow large enough to cause hyperthyroidism [110].

While the underlying mechanism of lower TSH levels increasing the risk of PTC is currently unclear, two genome-wide association studies have found that five common variants (rs965513[A] on 9q22.23, rs944289[T] and rs116909374[T] on 14q13.3, rs966423[C] on 2q35, and rs2439302[G] on 8p12) were associated with both an increased risk of thyroid cancer and low TSH level [111, 112]. According to Gudmundsson et al., the five variants could refer to genes FOXE1, NKX2-1, DIRC3, and NRG1. The FOXE1 gene can regulate the transcription of thyroglobulin and thyroperoxidase genes, and together with the NKX2-1 gene, plays an essential role in thyroid gland formation, differentiation, and function [113]. Although the function of the DIRC3 gene is unknown, it is presumed to have tumor suppressor activity [114]. The gene NRG1 encodes a signaling protein which mediates cell-cell interactions and plays a critical role in the growth and development of thyroid gland. The carriers of these five variants may be characterized by lower concentrations of TSH. The consequence of the lower TSH levels may be result in less differentiation of the thyroid epithelium, causing a higher predisposition to malignant cell transformation [112].

The present study observed positive associations in a dose-response manner between serum concentrations of TT3 and risk of PTC only among women. The observed inverse association between TSH levels and risk of PTC among women still held after excluding those ≥50 years old. These findings suggest that women may be more sensitive to the effect of TSH and thyroid hormones as compared to men. Possible explanations including effect modification of estrogen and
different exposure to endocrine disrupting chemicals (e.g., birth control pills and personal care products) by gender that need to be explored in future studies.

The present study also noted different associations of TSH and thyroid hormones on risk of PTC by histological subtype and tumor size. Lower TSH levels showed an association with increasing risk of the follicular variant of PTC and PTC >10mm, while higher TSH levels were associated with a decreased risk of classical PTC and PTC microcarcinoma. These associations may support the hypothesis that follicular variant of PTC and papillary microcarcinoma are unique clinical entities with different etiologic profiles [17, 115].

Additionally, the present study failed to find a clear pattern between TSH levels and risk of PTC with timing of the serum samples drawn. The relevant time window in which TSH exerts influence on development of thyroid cancer needs to be further studied.

The present study has several strengths. It included a relatively large number of male cases, providing sufficient statistical power to investigate and compare the associations by gender, which is important because women are much more likely to develop thyroid cancer than men. The study population was comprised entirely of US active duty military personnel, minimizing the potential differences in effects of TSH and thyroid hormones among healthy people and people with high risk of thyroid cancer. Potential selection bias from difference in access to medical care was also minimized for our study population. The serum concentrations of TSH and thyroid hormones were prospectively assessed and were not influenced by the disease process or treatment, which provided an opportunity to estimate potentially causal relationships between TSH, thyroid hormones, and thyroid cancer. A limitation of this study is that there was a lack of information on several potential confounding factors, such as ionizing radiation exposure, history of benign thyroid disease, family history of thyroid cancer, and smoking status. There were also a high percentage of participants
with missing BMI data, which may have led to insufficient adjustment for BMI. The lack of data on medication use preclude us from carrying out sensitivity analyses excluding people who were taking thyroid hormones. Furthermore, the subgroup analyses, which were stratified by years between samples collection and diagnosis, histological subtype, and tumor size, may have yielded unstable results due to the small subgroup counts.

In conclusion, the present study showed a significantly increased risk of PTC associated with TSH levels lower than the normal range among women and higher than the normal range among men. The observed associations varied by histological subtype and tumor size. These results could have significant clinical implications for physicians who are managing patients with abnormal thyroid functions and those with thyroidectomy. Future studies are warranted to further understand these associations.
Acknowledgments

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Conflict of interest

The authors declare they have no actual or potential conflict of interests.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Uniformed Services University of the Health Sciences, the Department of Defense, or the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the Department of Defense, the CDC, the Public Health Service, or the US Department of Health and Human Services.
Table 1. Distributions of selected characteristics among PTC cases and matched controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n=741)</th>
<th>Controls (n=741)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
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<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>210</td>
<td>28.3</td>
<td>203</td>
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<tr>
<td>30-39</td>
<td>309</td>
<td>41.7</td>
<td>322</td>
</tr>
<tr>
<td>40-49</td>
<td>185</td>
<td>25.0</td>
<td>179</td>
</tr>
<tr>
<td>≥50</td>
<td>37</td>
<td>5.0</td>
<td>37</td>
</tr>
<tr>
<td>Gender</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>400</td>
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<td>400</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>Race</td>
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<tr>
<td>Unknown</td>
<td>20</td>
<td>2.7</td>
<td>20</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>&lt;25</td>
<td>256</td>
<td>34.6</td>
<td>285</td>
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<tr>
<td>25-29.9</td>
<td>148</td>
<td>20.0</td>
<td>129</td>
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<tr>
<td>≥30</td>
<td>16</td>
<td>2.2</td>
<td>10</td>
</tr>
<tr>
<td>Missing</td>
<td>321</td>
<td>43.3</td>
<td>317</td>
</tr>
<tr>
<td>Service</td>
<td></td>
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<tr>
<td>Army</td>
<td>299</td>
<td>40.4</td>
<td>253</td>
</tr>
<tr>
<td>Air Force</td>
<td>193</td>
<td>26.1</td>
<td>150</td>
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<tr>
<td>Marines and Coast Guard combined</td>
<td>64</td>
<td>8.6</td>
<td>91</td>
</tr>
<tr>
<td>Navy</td>
<td>185</td>
<td>25.0</td>
<td>247</td>
</tr>
</tbody>
</table>

Abbreviation: PTC, Papillary Thyroid Cancer; BMI, Body Mass Index.
Figure 1. Risk of PTC associated with serum concentrations of TSH and thyroid hormones.

<table>
<thead>
<tr>
<th>TSH (µU/ml)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.30</td>
<td>28</td>
<td>11</td>
<td>2.65 (1.27-5.52)</td>
</tr>
<tr>
<td>0.30-1.19</td>
<td>280</td>
<td>230</td>
<td>1.37 (1.04-1.79)</td>
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<tr>
<td>1.20-1.93</td>
<td>215</td>
<td>230</td>
<td>1.00</td>
</tr>
<tr>
<td>1.94-4.20</td>
<td>166</td>
<td>236</td>
<td>0.75 (0.56-1.00)</td>
</tr>
<tr>
<td>&gt;4.20</td>
<td>51</td>
<td>34</td>
<td>1.58 (0.97-2.56)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td>0.90</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Total T3*** (ng/dl)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
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<tbody>
<tr>
<td>&lt;79</td>
<td>4</td>
<td>2</td>
<td>2.59 (0.45-14.80)</td>
</tr>
<tr>
<td>79-117</td>
<td>155</td>
<td>177</td>
<td>0.83 (0.61-1.12)</td>
</tr>
<tr>
<td>118-132</td>
<td>208</td>
<td>192</td>
<td>1.00</td>
</tr>
<tr>
<td>133-149</td>
<td>197</td>
<td>187</td>
<td>1.00 (0.75-1.34)</td>
</tr>
<tr>
<td>&gt;149</td>
<td>177</td>
<td>183</td>
<td>0.88 (0.64-1.21)</td>
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<tr>
<td>P for trend** (within the normal range)</td>
<td>0.031</td>
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<tr>
<td>P for trend** (overall)</td>
<td>0.18</td>
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<table>
<thead>
<tr>
<th>Total T4**** (µg/dl)</th>
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<th>Controls</th>
<th>OR* (95% CI)</th>
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<tbody>
<tr>
<td>&lt;5</td>
<td>4</td>
<td>3</td>
<td>1.12 (0.23-5.50)</td>
</tr>
<tr>
<td>5.7-7.7</td>
<td>209</td>
<td>196</td>
<td>1.21 (0.92-1.59)</td>
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<tr>
<td>7.8-8.8</td>
<td>203</td>
<td>232</td>
<td>1.00</td>
</tr>
<tr>
<td>8.9-10.6</td>
<td>214</td>
<td>224</td>
<td>1.06 (0.80-1.41)</td>
</tr>
<tr>
<td>&gt;10.6</td>
<td>110</td>
<td>86</td>
<td>1.39 (0.95-2.04)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td>0.46</td>
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<tr>
<th>Free T4***** (ng/dl)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.80</td>
<td>6</td>
<td>2</td>
<td>3.00 (0.56-16.20)</td>
</tr>
<tr>
<td>0.80-1.16</td>
<td>140</td>
<td>243</td>
<td>1.14 (0.86-1.50)</td>
</tr>
<tr>
<td>1.17-1.29</td>
<td>210</td>
<td>233</td>
<td>1.00</td>
</tr>
<tr>
<td>1.30-1.80</td>
<td>274</td>
<td>258</td>
<td>1.15 (0.88-1.52)</td>
</tr>
<tr>
<td>&gt;1.80</td>
<td>11</td>
<td>4</td>
<td>2.18 (0.59-8.05)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PTC: Papillary Thyroid Cancer; TSH: Thyroid-Stimulating Hormone; BMI: Body Mass Index.

*Conditional logistic regression, adjusted for BMI and branch of military service.

**Estimated by continuous variables.

***Additionally adjusted for serum concentration of TSH.
Figure 2. Risk of PTC associated with serum concentrations of TSH and thyroid hormones, stratified by gender.

<table>
<thead>
<tr>
<th>TSH (µIU/ml)</th>
<th>Male (n=800)</th>
<th>Female (n=652)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>&lt;0.30</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>0.30-1.19</td>
<td>131</td>
<td>109</td>
</tr>
<tr>
<td>1.20-1.93</td>
<td>125</td>
<td>123</td>
</tr>
<tr>
<td>1.54-4.20</td>
<td>103</td>
<td>145</td>
</tr>
<tr>
<td>&gt;4.20</td>
<td>37</td>
<td>19</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total T3*** (ng/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;79</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>79-117</td>
<td>96</td>
<td>101</td>
</tr>
<tr>
<td>118-132</td>
<td>133</td>
<td>119</td>
</tr>
<tr>
<td>133-149</td>
<td>116</td>
<td>101</td>
</tr>
<tr>
<td>&gt;149</td>
<td>52</td>
<td>77</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total T4**** (ng/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>5.7-7</td>
<td>149</td>
<td>126</td>
</tr>
<tr>
<td>7.8-8.8</td>
<td>121</td>
<td>141</td>
</tr>
<tr>
<td>8.9-10.6</td>
<td>110</td>
<td>111</td>
</tr>
<tr>
<td>&gt;10.6</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free T4***** (ng/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.80</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>0.80-1.16</td>
<td>110</td>
<td>99</td>
</tr>
<tr>
<td>1.17-1.29</td>
<td>107</td>
<td>121</td>
</tr>
<tr>
<td>1.30-1.80</td>
<td>176</td>
<td>177</td>
</tr>
<tr>
<td>&gt;1.80</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

| Abbreviation: PTC: Papillary Thyroid Cancer; TSH: Thyroid-Stimulating Hormone; BMI: Body Mass Index. |
| *Conditional logistic regression, adjusted for BMI and branch of military service. |
| **Estimated by continuous variables. |
| ***Additionally adjusted for serum concentration of TSH. |
Figure 3. Risk of PTC associated with serum concentrations of TSH and thyroid hormones among males, stratified by histological subtypes.

<table>
<thead>
<tr>
<th></th>
<th>Classical papillary (n=324)</th>
<th></th>
<th>Follicular variant papillary (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td>TSH (uU/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.50</td>
<td>2</td>
<td>4</td>
<td>0.77 (0.12-5.10)</td>
</tr>
<tr>
<td>0.50-1.19</td>
<td>105</td>
<td>109</td>
<td>1.07 (0.69-1.66)</td>
</tr>
<tr>
<td>1.20-1.94</td>
<td>95</td>
<td>123</td>
<td>1.00</td>
</tr>
<tr>
<td>1.94-4.20</td>
<td>87</td>
<td>145</td>
<td>0.60 (0.29-0.92)</td>
</tr>
<tr>
<td>&gt;4.20</td>
<td>35</td>
<td>19</td>
<td>1.94 (1.04-3.77)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td></td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Total T3*** (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;79</td>
<td>2</td>
<td>2</td>
<td>2.59 (0.21-31.25)</td>
</tr>
<tr>
<td>79.1-117</td>
<td>76</td>
<td>101</td>
<td>0.83 (0.53-1.29)</td>
</tr>
<tr>
<td>118-132</td>
<td>107</td>
<td>119</td>
<td>1.00</td>
</tr>
<tr>
<td>133-149</td>
<td>98</td>
<td>101</td>
<td>1.20 (0.78-1.83)</td>
</tr>
<tr>
<td>&gt;149</td>
<td>41</td>
<td>77</td>
<td>0.53 (0.30-0.94)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td></td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td></td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Total T4**** (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>3</td>
<td>2</td>
<td>1.76 (0.14-22.23)</td>
</tr>
<tr>
<td>5.7-7.7</td>
<td>120</td>
<td>126</td>
<td>1.32 (0.99-2.84)</td>
</tr>
<tr>
<td>7.8-8.8</td>
<td>98</td>
<td>141</td>
<td>1.09</td>
</tr>
<tr>
<td>8.9-10.6</td>
<td>89</td>
<td>111</td>
<td>1.07 (0.70-1.65)</td>
</tr>
<tr>
<td>&gt;10.6</td>
<td>14</td>
<td>20</td>
<td>1.18 (0.49-2.82)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td></td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td></td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Free T4***** (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.83</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0.80-1.16</td>
<td>88</td>
<td>99</td>
<td>1.07 (0.66-1.73)</td>
</tr>
<tr>
<td>1.17-1.29</td>
<td>89</td>
<td>121</td>
<td>1.00</td>
</tr>
<tr>
<td>1.30-1.80</td>
<td>141</td>
<td>177</td>
<td>0.99 (0.65-1.52)</td>
</tr>
<tr>
<td>&gt;1.80</td>
<td>3</td>
<td>3</td>
<td>1.71 (0.26-11.48)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td></td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td></td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PTC: Papillary Thyroid Cancer; TSH: Thyroid-Stimulating Hormone; BMI: Body Mass Index.

*Conditional logistic regression, adjusted for BMI and branch of military service.

**Estimated by continuous variables.

***Additionally adjusted for serum concentration of TSH.
Figure 4. Risk of PTC associated with serum concentrations of TSH and thyroid hormones among females, stratified by histological subtypes.

### Classical papillary (n=275)

<table>
<thead>
<tr>
<th>Serum TSH (µU/ml)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.30</td>
<td>21</td>
<td>7</td>
<td>2.72 (1.09-6.78)</td>
</tr>
<tr>
<td>0.30-1.19</td>
<td>109</td>
<td>121</td>
<td>1.09 (0.70-1.72)</td>
</tr>
<tr>
<td>1.20-1.93</td>
<td>80</td>
<td>107</td>
<td>1.00</td>
</tr>
<tr>
<td>1.94-4.20</td>
<td>52</td>
<td>91</td>
<td>0.69 (0.42-1.44)</td>
</tr>
<tr>
<td>&gt;4.20</td>
<td>12</td>
<td>15</td>
<td>0.93 (0.39-2.23)</td>
</tr>
</tbody>
</table>

P for trend** (within the normal range) 0.11
P for trend** (overall) 0.37

Total T3*** (ng/dl)

<table>
<thead>
<tr>
<th>Serum T3 (ng/dl)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;79</td>
<td>1</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>&gt;79</td>
<td>48</td>
<td>76</td>
<td>0.83 (0.48-1.42)</td>
</tr>
<tr>
<td>118-132</td>
<td>59</td>
<td>73</td>
<td>1.00</td>
</tr>
<tr>
<td>133-149</td>
<td>62</td>
<td>86</td>
<td>0.94 (0.56-1.60)</td>
</tr>
<tr>
<td>&gt;149</td>
<td>105</td>
<td>106</td>
<td>1.25 (0.76-2.09)</td>
</tr>
</tbody>
</table>

P for trend** (within the normal range) 0.13
P for trend** (overall) 0.021

Total T4**** (µg/dl)

<table>
<thead>
<tr>
<th>Serum T4 (µg/dl)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>1</td>
<td>1</td>
<td>1.20 (0.67-2.18)</td>
</tr>
<tr>
<td>5.7-7.7</td>
<td>53</td>
<td>70</td>
<td>1.14 (0.67-1.96)</td>
</tr>
<tr>
<td>7.8-8.8</td>
<td>65</td>
<td>91</td>
<td>1.10</td>
</tr>
<tr>
<td>8.9-10.6</td>
<td>83</td>
<td>113</td>
<td>1.12 (0.69-1.79)</td>
</tr>
<tr>
<td>&gt;10.6</td>
<td>72</td>
<td>66</td>
<td>1.55 (0.91-2.65)</td>
</tr>
</tbody>
</table>

P for trend** (within the normal range) 0.90
P for trend** (overall) 0.13

Free T4***** (ng/dl)

<table>
<thead>
<tr>
<th>Serum Free T4 (ng/dl)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.50</td>
<td>3</td>
<td>2</td>
<td>2.35 (0.54-11.07)</td>
</tr>
<tr>
<td>0.80-1.16</td>
<td>105</td>
<td>144</td>
<td>1.09 (0.72-1.65)</td>
</tr>
<tr>
<td>1.17-1.29</td>
<td>81</td>
<td>112</td>
<td>1.00</td>
</tr>
<tr>
<td>1.30-1.85</td>
<td>81</td>
<td>81</td>
<td>1.43 (0.85-2.42)</td>
</tr>
<tr>
<td>&gt;1.80</td>
<td>5</td>
<td>1</td>
<td>2.80 (0.27-28.91)</td>
</tr>
</tbody>
</table>

P for trend** (within the normal range) 0.32
P for trend** (overall) 0.2

### Follicular variant papillary (n=66)

<table>
<thead>
<tr>
<th>Serum TSH (µU/ml)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.31 (3.06-41.31)</td>
<td>3</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>10.10</td>
<td>40</td>
<td>121</td>
<td>—</td>
</tr>
<tr>
<td>1.00</td>
<td>10</td>
<td>107</td>
<td>—</td>
</tr>
<tr>
<td>2.31 (0.53-10.06)</td>
<td>11</td>
<td>91</td>
<td>—</td>
</tr>
<tr>
<td>4.92 (0.33-73.13)</td>
<td>2</td>
<td>15</td>
<td>—</td>
</tr>
</tbody>
</table>

*Estimated by continuous variables.
**Additionally adjusted for serum concentration of TSH.

Abbreviation: PTC: Papillary Thyroid Cancer; TSH: Thyroid-Stimulating Hormone; BMI: Body Mass Index.
*Conditional logistic regression, adjusted for BMI and branch of military service.
**Conditional logistic regression, adjusted for BMI and branch of military service.
***Estimated by continuous variables.
****Additionally adjusted for serum concentration of TSH.
Figure 5. Risk of PTC associated with serum concentrations of TSH and thyroid hormones among males, stratified by tumor size.

<table>
<thead>
<tr>
<th>Tumor size ≤10 mm (n = 115)</th>
<th>OR* (95% CI)</th>
<th>Tumor size &gt;10 mm (n = 262)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (μU/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.30</td>
<td>2.16 (0.17-27.82)</td>
<td>2</td>
<td>1.34 (0.15-12.03)</td>
</tr>
<tr>
<td>0.30-1.19</td>
<td>1.60 (0.74-3.49)</td>
<td>88</td>
<td>1.27 (0.79-2.05)</td>
</tr>
<tr>
<td>1.20-1.93</td>
<td>1.00</td>
<td>84</td>
<td>1.00</td>
</tr>
<tr>
<td>1.94-4.20</td>
<td>0.99 (0.47-2.12)</td>
<td>64</td>
<td>0.57 (0.35-0.92)</td>
</tr>
<tr>
<td>&gt;4.20</td>
<td>2.61 (0.71-9.34)</td>
<td>24</td>
<td>2.05 (0.91-4.62)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td>0.21</td>
<td></td>
<td>0.0003</td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td>0.76</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Total T3*** (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;79</td>
<td>1.24 (0.05-32.13)</td>
<td>2</td>
<td>2.89 (0.25-53.88)</td>
</tr>
<tr>
<td>79-117</td>
<td>0.62 (0.28-1.39)</td>
<td>62</td>
<td>1.07 (0.54-1.76)</td>
</tr>
<tr>
<td>118-132</td>
<td>1.00</td>
<td>85</td>
<td>1.00</td>
</tr>
<tr>
<td>133-149</td>
<td>0.70 (0.37-1.69)</td>
<td>81</td>
<td>1.22 (0.75-1.97)</td>
</tr>
<tr>
<td>&gt;149</td>
<td>0.38 (0.13-1.11)</td>
<td>32</td>
<td>0.72 (0.38-1.55)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td>0.93</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td>0.46</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Total T4*** (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>0.61 (0.01-14.40)</td>
<td>2</td>
<td>1.20 (0.06-22.69)</td>
</tr>
<tr>
<td>5.7-7</td>
<td>1.27 (0.63-2.55)</td>
<td>93</td>
<td>1.50 (0.96-2.34)</td>
</tr>
<tr>
<td>7.8-8.8</td>
<td>1.00</td>
<td>81</td>
<td>1.00</td>
</tr>
<tr>
<td>8.9-10.6</td>
<td>1.10 (0.45-2.66)</td>
<td>78</td>
<td>1.12 (0.49-1.81)</td>
</tr>
<tr>
<td>&gt;10.6</td>
<td>6.24 (0.78-49.92)</td>
<td>8</td>
<td>0.71 (0.26-1.99)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td>0.51</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td>0.56</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Free T4*** (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.80</td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>0.80-3.16</td>
<td>1.44 (0.56-3.69)</td>
<td>69</td>
<td>0.96 (0.57-1.62)</td>
</tr>
<tr>
<td>1.17-1.29</td>
<td>1.00</td>
<td>72</td>
<td>1.00</td>
</tr>
<tr>
<td>1.30-1.80</td>
<td>0.99 (0.45-2.20)</td>
<td>118</td>
<td>0.97 (0.61-1.55)</td>
</tr>
<tr>
<td>&gt;1.80</td>
<td>0.41</td>
<td>1</td>
<td>0.16 (0.01-3.96)</td>
</tr>
<tr>
<td>P for trend** (within the normal range)</td>
<td>0.41</td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>P for trend** (overall)</td>
<td>0.42</td>
<td></td>
<td>0.49</td>
</tr>
</tbody>
</table>

Abbreviation: PTC: Papillary Thyroid Cancer; TSH: Thyroid-Stimulating Hormone; BMI: Body Mass Index.

*Conditional logistic regression, adjusted for BMI and branch of military service.

**Estimated by continuous variables.

***Additionally adjusted for serum concentration of TSH.
Figure 6. Risk of PTC associated with serum concentrations of TSH and thyroid hormones among females, stratified by tumor size.

<table>
<thead>
<tr>
<th>TSH (μU/ml)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>Tumor size&gt; 10 mm (n=200)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
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</thead>
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<tr>
<td>&lt;0.20</td>
<td>7</td>
<td>7</td>
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<tr>
<td>0.30-1.19</td>
<td>44</td>
<td>121</td>
<td>2.47 (1.10-5.55)</td>
<td>94</td>
<td>121</td>
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<tr>
<td>1.20-1.93</td>
<td>29</td>
<td>107</td>
<td>1.00</td>
<td>57</td>
<td>107</td>
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<tr>
<td>1.94-4.20</td>
<td>34</td>
<td>91</td>
<td>1.60 (0.76-3.36)</td>
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<td>&gt;4.20</td>
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<td>P for trend** within the normal range</td>
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<td>0.977</td>
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<tr>
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<td>Total T3*** (ng/dl)</td>
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<td></td>
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<td>76</td>
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<td>1.18-1.52</td>
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<td>1.00</td>
<td>48</td>
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<tr>
<td>1.53-1.99</td>
<td>33</td>
<td>86</td>
<td>1.31 (0.56-3.05)</td>
<td>49</td>
<td>86</td>
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<tr>
<td>&gt;1.99</td>
<td>42</td>
<td>106</td>
<td>1.84 (0.85-4.02)</td>
<td>76</td>
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<td>0.032</td>
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<td>0.12</td>
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<tr>
<td>Total T4**** (μg/dl)</td>
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<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td>0.59 (0.24-1.47)</td>
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<td>7.8-8.8</td>
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<td>1.00</td>
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<td>0.97</td>
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<tr>
<td>Free T4***** (ng/dl)</td>
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<td></td>
<td>3</td>
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<td>1.24 (0.64-2.38)</td>
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<td>1.17-1.29</td>
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<td>1.41 (0.69-2.90)</td>
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<td>0.32 (0.08-1.26)</td>
<td>7</td>
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<tr>
<td>P for trend** within the normal range</td>
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<td></td>
<td>0.61</td>
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<tr>
<td>P for trend** (overall)</td>
<td>0.6</td>
<td></td>
<td></td>
<td>0.26</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviation: PTC: Papillary Thyroid Cancer; TSH: Thyroid-Stimulating Hormone; BMI: Body Mass Index.
*Conditional logistic regression, adjusted for BMI and branch of military service.
**Estimated by continuous variables.
***Additionally adjusted for serum concentration of TSH.
**Polybrominated Diphenyl Ethers, Polybrominated Biphenyls, and Peripheral Circulating Levels of Thyroid Hormones in Relation to Risk of Papillary Thyroid Cancer: A Nested Case-Control Study**

**Abstract**

*Background*: Emerging evidence has suggested that exposure to polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs) is related to disruption of thyroid hormone homeostasis. However, the effect of PBDEs and PBBs on serum levels of thyroid hormones is still inconclusive in human populations. Additionally, there is a lack of evidence pertaining to the mediation effect of thyroid hormones on the association between PBDEs/PBBs and risk of thyroid cancer.

*Methods*: The study population consisted of 741 (341 women, 400 men) histologically confirmed papillary thyroid cancer (PTC) cases and 741 matched controls with pre-diagnostic serum samples stored in the Department of Defense Serum Repository. Lipid-corrected serum concentrations of seven PBDE congeners and one PBB congener, as well as serum levels of thyroid-stimulating hormone (TSH), total T3 (TT3), total T4 (TT4), and free T4 (FT4) were measured in serum samples collected in two consecutive time points. Relationships between serum concentrations of PBDE and PBB congeners and hormone levels were examined by generalized additive models and linear regression models. Mediation effects of TSH on the association between PBDE and PBB congeners and risk of PTC were estimated by causal mediation analysis.

*Results*: Significantly nonmonotonic relationships were observed between serum concentrations of BDE-153 and BB-153 in relation to levels of TT3 and TT4 in PTC cases, and between BDE-47, -100, and -153 in relation to FT4 level in controls. The associations between PBDEs/PBBs and levels of TSH and thyroid hormones were stronger in cases than those in controls. Among cases,
higher serum concentrations of BDE-153 and BB-153 were associated with increased TSH level and decreased levels of TT3 and TT4, while higher concentration of BDE-100 was associated with reduced level of TSH and reduced level of TT4. The associations were varied by gender. Mediation effect of TSH accounts for a nonsignificant proportion in the total effect of PBDEs/PBBs on risk of PTC.

Conclusions: Results of this study contribute to the understanding of mechanisms underlying endocrine disrupting effect of PBDEs/PBBs. Further investigations using multiple longitudinal measurements and examining effect modification of genetic polymorphisms with PBDE alternatives among different populations are warranted to confirm these findings and identify high risk populations who are susceptible to these endocrine disrupting chemicals.

Keywords: polybrominated diphenyl ethers, polybrominated biphenyls, thyroid-stimulating hormone, thyroid hormone, causal mediation analysis
Polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs) belong to a class of brominated hydrocarbons that have been used as flame retardants globally in a variety of commercial and household products, including plastics, furniture, upholstery, textiles, electrical equipment, electronic devices, and other small appliances [29, 30]. PBDEs and PBBs are not single chemical compounds, but rather mixtures of different congeners with distinct brominated structures [29, 30]. The most important commercial mixtures of PBDE and PBB congeners are pentabromodiphenyl ethers (BDEs) (mainly composed of BDE-47 and -99), octa-BDEs (mainly composed of BDE-183, -197, and -209), deca-BDEs (mainly composed of BDE-209), and FireMaster BP-6 (mainly composed of BB-153) [116, 117]. Because PBDEs and PBBs are physically mixed into products as additives, rather than chemically bond with polymer resins, they have a potential to be released into the environment through production process or from products usage [21]. Due to their high lipophilicity, PBDEs and PBBs could also bioaccumulate and be biomagnified through food chains [23, 37, 118]. Humans could be exposed to environmental PBDEs and PBBs via inhalation, dust ingestion, and dietary intake [29, 30]. Since PBDEs and PBBs are persistent, with degradation half-lives in the order of years in the environment and in human bodies [22, 119, 120], these chemicals remain ubiquitous in the environment and are being detected in human populations even after discontinued production for years [19]. After a moderate decline of PBDE body burdens since approximately 2000 [54, 57], scientists have observed a significant increase in human serum concentrations of several PBDE congeners from 2011 to 2015 [32, 58]. Serum level of BB-153 among the Michigan residents exposed to PBBs in an accidental contamination of the food supply during 1973 and 1974 was still 10 times higher in 2012-2015, as compared to the 2011-2014 National Health and Nutrition Examination Survey (NHANES) data [121].

Emerging evidence indicates that exposure to PBDEs and PBBs is related to reduced circulating levels of thyroid hormones (i.e., triiodothyronine [T3] and thyroxine [T4]) in experimental animals
Two mechanisms have been suggested to explain the endocrine-disrupting effect of PBDEs. Since the chemical structures of PBDE congeners are similar to those of thyroid hormones, both hydroxylate and sulfate metabolites of PBDE congeners could competitively bind to thyroid hormone transport proteins (i.e., thyroxine-binding globulin [TBG] and transthyretin [TTR]) and nuclear receptors (i.e., ThRα and ThRβ) [19, 124-126]. The displacement of T4 from TTR and TBG may cause a higher glucuronidation rate and lower half-life of T4, resulting in a decreased circulating level of T4 [127]. The agonist/antagonist effects of PBDEs on thyroid hormone receptors may disrupt thyroid hormone signaling and lead to thyroid disfunction [128]. Additionally, PBDEs can induce the activity of major thyroid hormone metabolic enzymes, including cytochrome P450 isozymes (CYPs), uridine 5’-diphospho-glucuronosyltransferases (UDPGTs), sulfotransferases (SULTs), and deiodinases [19], and thus affect the metabolism of T3 and T4. The disruption of thyroid hormone homeostasis could further influence the secretion of thyroid-stimulating hormone (TSH) through a negative feedback loop on the hypothalamus-pituitary-thyroid axis. The mechanism underlying the association between PBBs and thyroid hormones is less clear. One speculated explanation is that PBBs exposure may cause an alteration of estrogen level and hence an increase in the synthesis of TBG [129, 130]. PBBs exposure has also been suggested to be able to alter the activity of deiodinases, and then affect the conversion of T4 to T3 [130].

Although animal studies indicate that exposure to PBDEs and PBBs is related to disruption of thyroid hormone homeostasis, evidence in human populations is still unestablished. Previous epidemiological studies yielded conflicting findings on the associations between PBDEs and PBBs exposure and thyroid hormone levels [55, 63, 130-139]. Some studies observed elevated levels of T3, T4, or TSH in relation to PBDEs exposure [131-134]; others reported inverse [133-137] or nonmonotonic [131] associations. A meta-analysis performed to estimate the effect of PBDEs exposure on serum levels of TSH and total T4 (TT4) reported substantial heterogeneities between
studies ($I^2 = 90.7\%$ and $57.6\%$ for TSH and TT4, respectively) [138]. Curtis and colleagues found that higher PBBs exposure before age 16 was associated with an increased level of T3 but a decreased level of T4 [130]. Studies on the relationship between PBBs and thyroid diseases also reported inconsistent results, with some observed positive association [55, 63], but the other found no association [139].

Several epidemiological studies have linked the risk of papillary thyroid cancer (PTC) in relation to PBDEs exposure [44, 140] and serum level of TSH [64, 68], respectively. If exposure to PBDEs could disrupt the homeostasis of thyroid hormones and then dysregulate TSH level, the thyroid carcinogenesis of PBDEs could operate through disruption of thyroid hormone homeostasis and fluctuation of TSH level. However, there is still lacking evidence pertaining to the mediation effect of TSH on the association between PBDEs/PBBs and risk of PTC.

Since it is biologically possible that PBDEs and PBBs could disrupt thyroid hormone homeostasis, but epidemiological evidence is still inconsistent, we conducted a nested case-control study using serum samples from the Department of Defense Serum Repository (DoDSR), with data from the Department of Defense (DoD) Automated Central Tumor Registry (ACTUR) and the Defense Medical Surveillance System (DMSS), to investigate the associations between serum concentrations of PBDEs and PBBs and levels of thyroid hormone. We also conducted a mediation analysis to estimate the potential mediation effect of serum level of TSH on the association between exposure to PBDEs and PBBs and risk of PTC.

Methods

Study population

Detailed information regarding the study design has been described elsewhere [64, 140] and in the Aim 1. In brief, 742 pairs of PTC cases diagnosed between 2000 and 2013 and non-cancer (except
for non-melanoma skin cancer) controls were enrolled from the US military personnel who had at least four serum samples drawn during active duty and stored in the DoDSR. Cases and controls were individually matched by date of birth (±1 year), gender, race/ethnicity, and midpoint of dates of selected four samples drawn (±1 year). All study procedures were approved by the Uniformed Services University Institutional Review Board, the Walter Reed National Military Medical Center, the DoD Joint Pathology Center, and the Human Investigation Committee of Yale University. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects research.

**Laboratory analyses**

Serum concentrations of PBDEs and PBBs were measured in the earliest pre-diagnostic serum samples. The measurement was conducted at the Persistent Organic Pollutants Laboratory, CDC (Atlanta, Georgia). The methodology used has been published [141] and the measured results have been summarized elsewhere [140]. Briefly, the analytical determinations of PBDE and PBB congeners were performed by using gas chromatography, isotope dilution, high-resolution mass spectrometry (GC-ID/HRMS) employing a DFS™ (Thermo Fisher Scientific, Waltham, Massachusetts) instrument. A total of 11 PBDE congeners (BDE-17, -28, -47, -66, -85, -99, -100, -153, -154, -183, and -209) and one PBB congener (BB-153) were measured. The levels of the 12 congeners were reported as lipid-corrected serum concentration (ng/g of serum lipid). Detection rates of PBDE and PBB congeners were similar among cases and controls (p-values from the χ² tests range: 0.089-0.90) [140].

Serum levels of TSH and thyroid hormones, including total T3 (TT3), TT4, and free T4 (FT4), were detected in the second earliest samples collected before cancer diagnosis. The measurement was performed by using electrochemiluminescence immunoassay at the Yale Medical Laboratory
The normal ranges for TSH, TT3, TT4, and FT4 were 0.3-4.2 mU/mL, 79-149 ng/dL, 5.0-10.6 mg/dL, and 0.80-1.80 ng/dL, respectively.

Statistical analyses

Because the laboratory measurements of TSH and thyroid hormones failed in one sample, all statistical analyses were conducted in the remaining 741 pairs of PTC cases and individually matched controls. Among the 12 congeners measured, seven PBDE congeners (BDE-28, -47, -85, -99, -100, -153, and -154) and one PBB congener (BB-153) that were detected in >20% of the control samples were included in the statistical analysis. Due to the right-skewed distribution, lipid-corrected serum concentrations of PBDE and PBB congeners and serum levels of TSH and thyroid hormones were compared between cases and controls using the Mann-Whitney U test, respectively.

Lipid-corrected serum concentrations of PBDE and PBB congeners that were below the limits of detection (LODs) were imputed as LOD/√2 for the correlation and regression analyses [142]. Lipid-corrected serum concentrations of PBDEs and PBB congeners were categorized into quartiles based on the distribution among controls, with the first quartile used as the reference category. Serum levels of TSH, TT3, TT4, and FT4 were divided into three categories on the basis of the normal range (i.e., below, within, and above the normal range). The correlations between serum concentrations of PBDE and PBB congeners and levels of TSH and thyroid hormones as continuous variables were estimated using the Pearson correlation coefficients. Kendall’s tau-b correlation coefficients were used to estimate the correlation between categorical levels of PBDE and PBB congeners, TSH, and thyroid hormones.

According to the scatter plots with smooth curve fitted by locally weighted smoothing (LOESS), relationships between serum concentrations of PBDE and PBB congeners and levels of TSH and thyroid hormones fitted nonmonotonic curves (Supplementary Figures 1-1 to 1-4). Thus,
generalized additive models (GAMs) were used to depict the potential nonlinear relationships. Linear regression was also conducted using the categorical levels of PBDE and PBB congeners to estimate effects of different concentration groups of congeners on hormone levels. TSH and thyroid hormones were natural log transformed in the GAMs and linear regression models to better fit a normal distribution. In the GAMs, serum concentrations of PBDE and PBB congeners were also natural log transformed, and one congener was included in each model. For the linear regression, all the categorical PBDE and PBB congeners were included in one model to additionally control for potential confounding effect from other congeners. Other confounding variables include body mass index (BMI; <18.5, 18.5-24.9, 25-29.9, and 30 kg/m²) and branch of military service (army, air force, marines and coast guard, and navy). Relationships between serum concentrations of PBDE and PBB congeners and levels of TSH and thyroid hormones were examined in cases and controls, respectively. Stratified analyses were also performed by gender to investigate if estrogen impacts the relationships.

Mediation effects of TSH on the association between PBDE and PBB congeners and risk of PTC were estimated by applying the R package mediation, which is recommended as a flexible and statistically powerful approach to conduct causal mediation analysis [143]. By performing this analysis, the average causal mediation effect (ACME) (i.e., effect of TSH on the risk of PTC) and the average direct effect (ADE) (i.e., effect of PBDEs/PBBs on the risk of PTC that not through alternation of TSH) could be distinguished and reported separately. The ACME was estimated using hierarchical linear model, and the ADE was evaluated by generalized linear mixed-effects model. Both models were adjusted for all PBDE and PBB congeners, BMI, and branch of military service. The proportion of mediation effect in the total effect was estimated by \( \frac{ACME}{ADE + ACME} \). The causal mediation analysis was also conducted in classical PTC and large tumors (>10 mm) and was stratified by gender, according to the observed associations between BDE-28, TSH, and risk of PTC in our previous studies [64, 140].
All tests were 2-sided with $\alpha=0.05$. Because seven PBDE and one PBB congeners were included in the final analysis, a Bonferroni-adjusted $\alpha$ of 0.05/8=0.006 was applied to control for multiple comparisons. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc.; Cary, North Carolina) and R, version 3.6.3 (R Foundation, Vienna, Austria).

Results

Serum samples used for the measurement of PBDEs and PBBs were drawn during 1994 to 2009 and approximately 3.1-12.0 years before the cases were diagnosed with PTC, while the samples used for measuring TSH and thyroid hormones were collected approximately 0.2-11.6 years before cancer diagnosis. The intervals between these two sampling dates were ranged from 0.1 to 12.1 years, with the median of 2.6 years (interquartile range [IQR]=1.4-4.6 years) (data not shown).

Except for TSH, distributions of serum concentrations of PBDE and PBB congeners and serum levels of thyroid hormones were similar among cases and controls ($p$-values from the Mann-Whitney U tests range: 0.27-0.76) (Table 1). TSH level was significantly lower in cases than that in controls ($P=0.0004$). The Pearson correlation coefficients indicated that serum concentrations of PBDE congeners as continuous values were strongly correlated with each other (Pearson's $r$ range: 0.51-0.98), but the correlations between PBDE congeners and PBB-153 were very weak ($|$Pearson's $r| <0.01$) (Supplementary Table 1). Compared with the continuous values, the correlations between categorical concentrations of PBDE congeners were weakened (Kendall's $\tau$ range: 0.40-0.90) (Supplementary Table 2). Serum levels of TSH and thyroid hormones were just weakly correlated with PBDE and PBB congeners ($|$Pearson's $r| <0.1$ and $|$Kendall's $\tau| <0.2$) (Supplementary Tables 1 and 2).
Based on results of the GAMs, nonmonotonic relationships were observed between serum concentrations of BDE-153 and BB-153 and levels of TT3 (P=0.033 and 0.0072 with BDE-153 and BB-153, respectively) and TT4 (P=0.011 and 0.0010 with BDE-153 and BB-153, respectively) in PTC cases (Supplementary Figures 2-2 and 2-3). The effects of BDE-47 (P=0.0088), -100 (P=0.0051), and -153 (P=0.025) on FT4 level were nonmonotonic in controls (Supplementary Figure 3-4).

Results from the linear regression models showed stronger associations between serum concentrations of PBDE and PBB congeners and levels of TSH and thyroid hormones in PTC cases as compared to controls. Among cases, higher serum concentrations of BDE-153 and BB-153 were associated with increased TSH level and decreased levels of TT3 and TT4, while higher concentration of BDE-100 was associated with reduced level of TSH and elevated level of TT4 (Figure 1). After Bonferroni correction, the associations between BDE-153 in relation to levels of TSH (β=0.63, 95% confidence interval [CI]: 0.29, 0.98 for the Q4 vs. Q1), TT3 (β=-0.11, 95% CI: -0.19, -0.04 for the Q4 vs. Q1), and TT4 (β=-0.10, 95% CI: -0.17, -0.03 for the Q4 vs. Q1) and between BB-153 in relation to levels of TT3 (β=-0.06, 95% CI: 0.01, -0.11, -0.02 for both Q3 vs. Q1) and TT4 (β=-0.08, 95% CI: -0.13, -0.04 for the Q4 vs. Q1) remained significant (data not shown). But in controls, only higher concentration of BB-153 was suggestively associated with a reduced level of TT4 (β=-0.046, 95% CI: -0.088, -0.005 for the Q4 vs. Q1), and this association was no longer significant after Bonferroni correction (Figure 2). The associations between concentrations of BDE-100, -153, and BB-153 in relation to TSH level were statistically stronger in cases than those in controls (P\text{interaction}=0.0004, 0.0024, and 0.0099, respectively) (data not shown). When stratified the analysis in cases by gender, the associations between higher concentration of BDE-100 in relation to decreased level of TSH and increased level of TT4 was only observed among men (P\text{interaction}=0.0002 and <0.0001, respectively), while the positive association between higher concentration of BDE-153 and TSH level, as well as the inverse associations between higher
concentrations of BDE-153 and BB-153 in relation to levels of TT3 and TT4 were observed among women, but not among men (P_{interaction}=0.0006 for BDE-153 and TSH; 0.0014 for BDE-153 and TT3; <0.0001 for BDE-153 and TT4; 0.0008 for BB-153 and TT3; and <0.0001 for BB-153 and TT4) (Figure 3).

According to results from the causal mediation analysis, the ADE of BED-28 on increasing risk of large classical PTC (>10 mm) was statistically significant, and this effect is especially dominant in women. However, neither the ACME of TSH nor the proportion of mediation effect in the total effect are significant (Table 2). In addition, the mediation effect of TSH accounts for a nonsignificant proportion in the total effect of other PBDE and PBB congeners on the risk of PTC (Supplementary Table 3).

**Discussion**

This study observed significantly nonmonotonic relationships between serum concentrations of BDE-153 and BB-153 and levels of TT3 and TT4 in PTC cases, and between BDE-47, -100, and -153 in relation to FT4 level in controls. The associations between PBDEs/PBBs and levels of TSH and thyroid hormones were stronger in cases than those in controls. Among cases, higher serum concentrations of BDE-153 and BB-153 were associated with increased level of TSH and decreased levels of TT3 and TT4, while higher concentration of BDE-100 was associated with reduced level of TSH and elevated level of TT4. When stratified by gender, the effects of BDE-100 on levels of TSH and TT4 were only observed among men, while the effects of BDE-153 and BB-153 on levels of TT3 and TT4 were only observed among women. Results from the causal mediation analysis did not support the hypothesis that the thyroid carcinogenesis of PBDEs/PBBs is mainly operated through disruption of thyroid hormone homeostasis and fluctuation of TSH level.
The geometric means of concentrations for BDE-28, -47, -99, -100, -153, and BB-153 in controls of this study (Table 1) were higher than those in the US general population from the NHANES 2003-2004 [56]. 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 2003/04 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 2003/04 population, indicating a more centralized range of concentrations in the current military population as compared to the NHANES general population. A similar range of concentrations was only observed for BDE-153 between the study population and NHANES 2003/04 population. The distributions of serum levels of TSH and thyroid hormones in majority of this study population were within the normal ranges (94% for TSH; 75% for TT3; 88% for TT4; and 99% for FT4 in controls) (data not shown).

The significant associations between serum concentrations of BDE-100 and -153 in relation to levels of TSH and thyroid hormones from the current study are partially similar to those observed in several previous studies [133, 136, 137], but other studies did not report significant associations with these PBDE congeners [132, 134, 135]. The disparities between studies may be caused by the nonmonotonic relationships between PBDE congeners and levels of TSH and thyroid hormones. Due to the nature of nonmonotonicity, associations were varied with different concentrations of PBDEs. For example, Guo and colleagues investigated the associations between PBDEs and thyroid hormones in 174 school students lived near a petrochemical complex in South China, and did not find any significant associations with BDE-153 [131]. In this Chinese student population, serum concentrations of BDE-153 was lower than that in the highest quartile of our study population (median [range]: 2.9 [6.0-25.0] ng/g lipid vs. 27.0 [11.5-285.5] ng/g lipid). The associations between lower concentration of BDE-153 and levels of TSH and thyroid hormones were also nonsignificant in our study population. A meta-analysis performed to estimate the
association between PBDEs exposure and thyroid hormone levels suggested that the effects of PBDE congeners depend on their degree of bromination and inner concentrations [138]. The meta-analysis also reported an approximate U-shaped relationship between PBDEs exposure and changes in thyroid hormone levels. Lower concentration of $\sum$PBDEs (median level <30 ng/g lipids) was associated with reduced serum level of TSH, while higher concentration (median level >100 ng/g lipids) was associated with elevated serum level of TSH. Similarly, serum level of TT4 was negatively associated with lower $\sum$PBDEs concentration (median level <35 ng/g lipids) and positively associated with higher PBDEs concentration (median level between 35 and 100 ng/g lipids) [138]. In the current study, we also observed a statistically significant U-shaped relationship between BDE-153 and TT4 in cases (P=0.011) (Supplementary Figure 2-3).

Variations in study populations and geometric distributions may also contribute to the heterogeneity between studies. Previous studies included school children [131, 135], pregnant women [132, 137], e-waste recycling workers [134], and residents living near a petrochemical complex [131] or a e-waste dismantling area [135, 136]. The circulating levels of TSH and thyroid hormones are significantly higher in children than those in adults [144, 145]. These physiological changes in thyroid gland and impact of placental human chorionic gonadotropin (hCG) during pregnancy may result in increased T3 and T4 and decreased TSH [146]. A review on human exposure to PBDEs in e-waste areas indicated that the residents and some vulnerable groups (e.g., occupational workers and children) in e-waste recycling areas may face higher exposure levels as compared to people living in other areas [147]. The variance in thyroid hormone levels and PBDEs exposure may partially explain the different observed relationships.

According to the meta-analysis on the relationships between PBDEs and thyroid hormones, duration of exposure may also affect the effects of PBDEs [138]. The analyses stratified by intervals between sample dates for congeners and hormones (≤3 and >3 years; based on sample size)
suggested a significantly positive association between higher serum concentration of BDE-28 and TSH level in samples collected for >3 years ($\beta=1.31$, 95% CI: 0.45, 2.17 for the Q4 vs. Q1), but a nonsignificant negative association in samples collected for ≤3 years ($\beta=-0.32$, 95% CI: -0.83, 0.19 for the Q4 vs. Q1) (data not shown). The effects of PBDEs on thyroid hormone levels by duration of exposure need to be further investigated by longitudinal measurements.

Our study observed significant relationship between BB-153 and serum levels of TSH, TT3, and TT4, which was not reported by previous studies. One cross-sectional study in 715 participants of the Michigan PBB Registry reported a negative association between $\Sigma$PBBs and FT4, but nonsignificant relationships with TSH, TT3, and TT4 [130]. Since previous studies on PBBs were mainly conducted in the Michigan residents, whose exposure level was substantially higher than other populations due to an accidental contamination of the food supply during 1973 and 1974 [55, 56, 121], the observed associations with PBB-153 in the DoDSR cohort need to be verified in other general populations. Previous studies suggested an estrogenic effect of PBBs, and speculated that the altered estrogen levels by PBBs exposure may affect the synthesis of TBG, which is a thyroid hormone transport protein that is able to bind the majority of T4 [129, 130]. In the current study, the effect of BB-153 on thyroid hormone levels was observed only among women, but not among men.

This study did not find any evidence supporting a mediation effect of TSH on the association between PBDEs/PBBs and risk of PTC. After examining the carcinogenetic effect of PBDEs/PBBs on the risk of PTC by TSH level, an interaction between PBDEs/PBBs and TSH on PTC risk was not suggested as well (data not shown). Thus, the mechanisms underlying the potential thyroid carcinogenicity of PBDEs/PBBs need to be further explored in future mechanistic studies.
The present study has several strengths. The sample size was relatively large, providing sufficient statistical power to investigate and compare the relationships by gender. Although we did not suspect a specific source of exposure to PBDEs related to military service, PBDEs are persistent, with half-lives range between 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 serum concentrations of PBDE and PBB congeners and levels of TSH and thyroid hormones were respectively assessed in two serum samples collecting consecutively before cancer diagnosis, which provides an opportunity to estimate potentially causal relationships between exposure to PBDEs/PBBs and thyroid hormone homeostasis, without being influenced by the disease process or treatment.

Limitations should be considered when interpreting results of this study. There was a high percentage of participants with missing BMI data, which may have led to insufficient adjustment for BMI. Previous evidence has suggested lower prevalence of obesity and larger lean body mass of military personnel than the US civilian population [69], indicating less variation of BMI among the US military personnel. Thus, any effect of under-adjustment for BMI would likely be minimized in this study population. PBDEs/PBBs and thyroid hormones were measured in one-time serum samples, respectively. Misclassifications of inner levels of chemicals and hormones cannot be ruled out. Additionally, any changes in relationships by duration of exposure were not able to be captured in this study. The lack of data on medication use preclude us from carrying out sensitivity analyses excluding people who were taking thyroid hormones. Furthermore, the stratified analyses may have yielded unstable results due to the reduced subgroup counts. It is also possible that the relationships were observed by chance due to the multiple comparisons. However, the effects of BDE-153 and BB-153 on TSH and thyroid hormones remained statistically significant after Bonferroni adjustment, indicating a true association.
In conclusion, this study suggested significant disrupting effects of BDE-100, 153, and BB-153 on serum levels of TSH and thyroid hormones. The observed relationships were nonmonotonic and varied by gender. Results from the causal mediation analysis did not support a mediation effect of TSH on the association between PBDEs/PBBs and risk of PTC. Findings of this study contribute to the understanding of mechanisms underlying endocrine disrupting effect of PBDEs/PBBs. Further investigations using multiple longitudinal measurements and examining effect modification of genetic polymorphisms is warranted. Additionally, more epidemiological studies with PBDE alternatives among different populations are also warranted to confirm these findings and identify high risk populations who are susceptible to these endocrine disrupting chemicals.
Acknowledgments

Grant Support

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Conflict of interest

The authors declare they have no actual or potential conflict of interests.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Uniformed Services University of the Health Sciences, the Department of Defense, or the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the Department of Defense, the CDC, the Public Health Service, or the US Department of Health and Human Services.
Table 1. Lipid-corrected serum concentrations of PBDE and PBB congeners (ng/g) and serum levels of TSH and thyroid hormones among PTC cases and controls.

<table>
<thead>
<tr>
<th>Congener</th>
<th>LOD a Median (IQR)</th>
<th>Detected b No.</th>
<th>Detected b %</th>
<th>GM (GSD)</th>
<th>Median (IQR)</th>
<th>Cases</th>
<th>Controls</th>
<th>Detected b No.</th>
<th>Detected b %</th>
<th>GM (GSD)</th>
<th>Median (IQR)</th>
<th>P-value c</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDE-28</td>
<td>1.1 (0.9-1.3)</td>
<td>250</td>
<td>33.7</td>
<td>3.0 (2.5)</td>
<td>&lt;LOD (&lt;LOD-1.5)</td>
<td>236</td>
<td>31.9</td>
<td>2.6 (2.3)</td>
<td>&lt;LOD (&lt;LOD-1.5)</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDE-47</td>
<td>2.5 (2.1-2.8)</td>
<td>707</td>
<td>95.4</td>
<td>21.5 (3.7)</td>
<td>16.3 (7.9-38.7)</td>
<td>706</td>
<td>95.3</td>
<td>21.0 (3.2)</td>
<td>16.8 (8.4-38.3)</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDE-85</td>
<td>1.0 (0.8-1.3)</td>
<td>208</td>
<td>28.1</td>
<td>3.3 (3.0)</td>
<td>&lt;LOD (&lt;LOD-1.0)</td>
<td>203</td>
<td>27.4</td>
<td>2.8 (2.6)</td>
<td>&lt;LOD (&lt;LOD-1.0)</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDE-99</td>
<td>2.0 (1.7-2.4)</td>
<td>548</td>
<td>74.0</td>
<td>9.1 (3.6)</td>
<td>4.3 (&lt;LOD-10.6)</td>
<td>576</td>
<td>77.7</td>
<td>8.2 (3.2)</td>
<td>4.4 (2.2-10.6)</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDE-100</td>
<td>1.0 (0.9-1.3)</td>
<td>620</td>
<td>83.7</td>
<td>5.7 (3.5)</td>
<td>3.4 (1.5-8.8)</td>
<td>642</td>
<td>86.6</td>
<td>5.3 (3.0)</td>
<td>3.7 (1.8-8.6)</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDE-153</td>
<td>1.0 (0.8-1.3)</td>
<td>678</td>
<td>91.5</td>
<td>6.4 (3.4)</td>
<td>4.4 (2.1-11.5)</td>
<td>690</td>
<td>93.1</td>
<td>6.3 (3.0)</td>
<td>4.6 (2.5-11.3)</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDE-154</td>
<td>1.0 (0.9-1.3)</td>
<td>217</td>
<td>29.3</td>
<td>3.0 (2.9)</td>
<td>&lt;LOD (&lt;LOD-1.1)</td>
<td>209</td>
<td>28.2</td>
<td>2.6 (2.5)</td>
<td>&lt;LOD (&lt;LOD-1.0)</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB-153</td>
<td>1.0 (0.9-1.3)</td>
<td>543</td>
<td>73.3</td>
<td>3.0 (2.3)</td>
<td>2.0 (&lt;LOD-3.5)</td>
<td>549</td>
<td>74.1</td>
<td>3.1 (2.2)</td>
<td>2.1 (0.9-3.6)</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TSH (µU/mL) | 1.3 (2.8) | 1.4 (0.9-2.1) | 1.5 (1.9) | 1.6 (1.1-2.3) | 0.0004 |
TT3 (ng/dL) | 134.3 (1.2) | 130.0 (120.0-148.0) | 132.4 (1.2) | 132.0 (118.0-149.0) | 0.50 |
TT4 (µg/dL) | 8.7 (1.2) | 8.6 (7.6-9.8) | 8.6 (1.2) | 8.6 (7.7-9.6) | 0.76 |
FT4 (ng/dL) | 1.2 (1.2) | 1.3 (1.1-1.4) | 1.2 (1.1) | 1.2 (1.1-1.4) | 0.33 |

Abbreviations: Abbreviations: PBDE, polybrominated diphenyl ether; PBB, polybrominated biphenyl; TSH, thyroid-stimulating hormone; PTC, papillary thyroid cancer; LOD: limit of detection; IQR, interquartile range; GM, geometric mean; GSD, geometric standard deviation; BDE-28, 2,4',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; BB-153, 2,2',4,4',5,5'-hexabromobiphenyl; TT3, total triiodothyronine; TT4, total thyroxine; FT4, free thyroxine.

a Calculated among cases and controls combined.
b Serum samples containing PBDE or PBB congener had an amount above the LOD, and the value of concentration is detectable.
c Estimated by the Mann-Whitney U test.
Table 2. Mediation effect of TSH on the association between lipid-corrected serum concentration of BDE-28 (ng/g) and risk of PTC.

<table>
<thead>
<tr>
<th>BDE-28</th>
<th>Overall PTC</th>
<th>Classical PTC</th>
<th>Large classical PTC (&gt;10 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEM</td>
<td>ADE</td>
<td>Prop. of Mediation</td>
</tr>
<tr>
<td>&lt;LOD</td>
<td>ref.</td>
<td>ref.</td>
<td>ref.</td>
</tr>
<tr>
<td>&gt;LOD-1.56</td>
<td>-0.0025</td>
<td>-0.0139</td>
<td>0.0136</td>
</tr>
<tr>
<td>1.57-3.18</td>
<td>-0.0036</td>
<td>0.0597</td>
<td>-0.0323</td>
</tr>
<tr>
<td>3.19-80.10</td>
<td>-0.0059</td>
<td>0.1054</td>
<td>-0.0404</td>
</tr>
</tbody>
</table>

Abbreviation: TSH, thyroid-stimulating hormone; BDE-28, 2,4,4’-tribromodiphenyl ether; PTC, papillary thyroid cancer; ACEM, average causal mediation effect; ADE, average direct effect; LOD: limit of detection; BMI, body mass index.

Hierarchical linear model and generalized linear mixed-effects model, adjusted for all PBDE and PBB congeners, BMI, and branch of military service.

*P-value <0.05.

**P-value <0.01.

***P-value <0.001.
Figure 1. Estimated effects of categorical serum concentrations of PBDE and PBB congeners on natural log transformed serum levels of TSH (A), TT3 (B), TT4 (C), and FT4 (D) in PTC cases, using linear regression models adjusted for all PBDE and PBB congeners, BMI, and branch of military service.
Figure 2. Estimated effects of categorical serum concentrations of PBDE and PBB congeners on natural log transformed serum levels of TSH (A), TT3 (B), TT4 (C), and FT4 (D) in controls, using linear regression models adjusted for all PBDE and PBB congeners, BMI, and branch of military service.
Figure 3. Estimated effects of categorical serum concentrations of PBDE and PBB congeners on natural log transformed serum levels of TSH, TT3, TT4, and FT4 in male PTC cases (A) and female PTC cases (B), using linear regression models adjusted for all PBDE and PBB congeners, BMI, and branch of military service.
Supplementary Table 1. Pearson correlation coefficients between continuous serum concentrations of PBDE and PBB congeners, TSH, and thyroid hormones.

<table>
<thead>
<tr>
<th></th>
<th>BDE-28</th>
<th>BDE-47</th>
<th>BDE-85</th>
<th>BDE-99</th>
<th>BDE-100</th>
<th>BDE-153</th>
<th>BDE-154</th>
<th>BB-153</th>
<th>TSH</th>
<th>TT3</th>
<th>TT4</th>
<th>FT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDE-28</td>
<td>1</td>
<td>0.9338**</td>
<td>0.8928**</td>
<td>0.8483**</td>
<td>0.8959**</td>
<td>0.5828**</td>
<td>0.8840**</td>
<td>-0.0042</td>
<td>-0.0139</td>
<td>-0.0320</td>
<td>-0.0286</td>
<td>-0.0509</td>
</tr>
<tr>
<td>BDE-47</td>
<td></td>
<td>1</td>
<td>0.9728**</td>
<td>0.9470**</td>
<td>0.9511**</td>
<td>0.5908**</td>
<td>0.9482**</td>
<td>0.0011</td>
<td>-0.0166</td>
<td>-0.0259</td>
<td>-0.0150</td>
<td>-0.0470</td>
</tr>
<tr>
<td>BDE-85</td>
<td></td>
<td></td>
<td>1</td>
<td>0.9718**</td>
<td>0.9360**</td>
<td>0.5821**</td>
<td>0.9761**</td>
<td>-0.0036</td>
<td>-0.0207</td>
<td>-0.0258</td>
<td>-0.0119</td>
<td>-0.0468</td>
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<tr>
<td>BDE-99</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.8795**</td>
<td>0.5115**</td>
<td>0.9542**</td>
<td>-0.0050</td>
<td>-0.0140</td>
<td>-0.0304</td>
<td>-0.0174</td>
<td>-0.0471</td>
</tr>
<tr>
<td>BDE-100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.7424**</td>
<td>0.9511**</td>
<td>-0.0003</td>
<td>-0.0119</td>
<td>-0.0291</td>
<td>-0.0214</td>
<td>-0.0451</td>
</tr>
<tr>
<td>BDE-153</td>
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<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.6322**</td>
<td>-0.0025</td>
<td>0.0010</td>
<td>-0.0442</td>
<td>-0.0271</td>
<td>-0.0095</td>
</tr>
<tr>
<td>BDE-154</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>-0.0054</td>
<td>-0.0152</td>
<td>-0.0302</td>
<td>-0.0146</td>
<td>-0.0477</td>
</tr>
<tr>
<td>BB-153</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.0148</td>
<td>-0.0223</td>
<td>-0.0481</td>
<td>-0.0237</td>
</tr>
<tr>
<td>TSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>-0.0596*</td>
<td>-0.1720**</td>
<td>-0.1896**</td>
</tr>
<tr>
<td>TT3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.6806**</td>
<td>0.3954**</td>
</tr>
<tr>
<td>TT4</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.5164**</td>
</tr>
<tr>
<td>FT4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; TSH, thyroid-stimulating hormone; 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; BB-153, 2,2',4,4',5,5'-hexabromobiphenyl; TT3, total triiodothyronine; TT4, total thyroxine; FT4, free thyroxine.

*P-value <0.05.

**P-value <0.0001.
Supplementary Table 2. Kendall’s tau-b correlation coefficients between categorical serum concentrations of PBDE and PBB congeners, TSH, and thyroid hormones.

<table>
<thead>
<tr>
<th></th>
<th>BDE-28</th>
<th>BDE-47</th>
<th>BDE-85</th>
<th>BDE-99</th>
<th>BDE-100</th>
<th>BDE-153</th>
<th>BDE-154</th>
<th>BB-153</th>
<th>TSH</th>
<th>TT3</th>
<th>TT4</th>
<th>FT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDE-28</td>
<td>1</td>
<td>0.5401**</td>
<td>0.7339**</td>
<td>0.4647**</td>
<td>0.5193**</td>
<td>0.4049**</td>
<td>0.7395**</td>
<td>0.1025**</td>
<td>0.0030</td>
<td>0.0001</td>
<td>-0.0163</td>
<td>-0.0364</td>
</tr>
<tr>
<td>BDE-47</td>
<td>1</td>
<td>0.4516**</td>
<td>0.8150**</td>
<td>0.8223**</td>
<td>0.5531**</td>
<td>0.4644**</td>
<td>0.0857**</td>
<td>-0.0333</td>
<td>-0.0029</td>
<td>-0.0165</td>
<td>-0.0266</td>
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<tr>
<td>BDE-85</td>
<td>1</td>
<td>0.4525**</td>
<td>0.4641**</td>
<td>0.3965**</td>
<td>0.8992**</td>
<td>0.0432*</td>
<td>-0.0314</td>
<td>0.0191</td>
<td>-0.0001</td>
<td>-0.0045</td>
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</tr>
<tr>
<td>BDE-99</td>
<td>1</td>
<td>0.7764**</td>
<td>0.5369**</td>
<td>0.4531**</td>
<td>0.0709*</td>
<td>-0.0386</td>
<td>0.0136</td>
<td>-0.0112</td>
<td>-0.0351</td>
<td></td>
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<tr>
<td>BDE-100</td>
<td>1</td>
<td>0.6891**</td>
<td>0.4951**</td>
<td>0.0893**</td>
<td>-0.0356</td>
<td>-0.0016</td>
<td>-0.0156</td>
<td>-0.0139</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDE-153</td>
<td>1</td>
<td>0.4260**</td>
<td>0.0891**</td>
<td>-0.0015</td>
<td>-0.0391</td>
<td>-0.0361</td>
<td>-0.0137</td>
<td></td>
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<td></td>
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<tr>
<td>BDE-154</td>
<td>1</td>
<td>0.0731*</td>
<td>-0.0253</td>
<td>0.0155</td>
<td>-0.0066</td>
<td>-0.0426</td>
<td></td>
<td></td>
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<tr>
<td>BB-153</td>
<td>1</td>
<td>0.0455</td>
<td>-0.1062**</td>
<td>-0.1434**</td>
<td>-0.0181</td>
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<tr>
<td>TSH</td>
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<td>-0.0942*</td>
<td>-0.1472**</td>
<td>-0.2564**</td>
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<tr>
<td>TT3</td>
<td>1</td>
<td>0.4681**</td>
<td>0.1081**</td>
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<tr>
<td>TT4</td>
<td>1</td>
<td>0.2954**</td>
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</table>

Abbreviations: PBDE, polybrominated diphenyl ether; PBB, polybrominated biphenyl; TSH, thyroid-stimulating hormone; 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; BB-153, 2,2',4,4',5,5'-hexabromobiphenyl; TT3, total triiodothyronine; TT4, total thyroxine; FT4, free thyroxine.

*P-value <0.05.

**P-value <0.0001.
Supplementary Table 3. Mediation effect of TSH and on the association between lipid-corrected serum concentrations of PBDE and PBB congeners (ng/g) and risk of PTC.

<table>
<thead>
<tr>
<th>Overall PTC</th>
<th>Classical PTC</th>
<th>Large classical PTC (&gt;10 mm)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>ACEM</td>
<td>ADE</td>
</tr>
<tr>
<td>BDE-47</td>
<td>&lt;LOD-8.43</td>
<td>ref.</td>
</tr>
<tr>
<td>8.44-16.91</td>
<td>-0.0027</td>
<td>0.0487</td>
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<tr>
<td>16.92-38.63</td>
<td>-0.0069</td>
<td>0.0606</td>
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<tr>
<td>38.64-2189.00</td>
<td>0.0090</td>
<td>0.0097</td>
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<tr>
<td>BDE-85</td>
<td>&lt;LOD</td>
<td>ref.</td>
</tr>
<tr>
<td>&gt;LOD-1.68</td>
<td>-0.0012</td>
<td>0.0263</td>
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<tr>
<td>1.69-3.18</td>
<td>-0.0062</td>
<td>-0.1448</td>
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<td>3.19-79.08</td>
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<tr>
<td>BDE-99</td>
<td>&lt;LOD-2.17</td>
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<td>2.18-4.40</td>
<td>0.0012</td>
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<tr>
<td>4.41-10.61</td>
<td>0.0062</td>
<td>-0.0204</td>
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<tr>
<td>10.62-993.30</td>
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<td>-0.0270</td>
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<tr>
<td>BDE-100</td>
<td>&lt;LOD-1.84</td>
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<td>1.85-3.71</td>
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<td>-0.0828</td>
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<tr>
<td>3.72-8.65</td>
<td>0.0107</td>
<td>-0.1232</td>
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<td>8.66-368.00</td>
<td>0.0140</td>
<td>-0.0966</td>
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<td>BDE-153</td>
<td>&lt;LOD-2.49</td>
<td>ref.</td>
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<tr>
<td>2.50-4.61</td>
<td>-0.0086*</td>
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<td>4.62-11.23</td>
<td>-0.0077</td>
<td>-0.0332</td>
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<td>11.24-285.50</td>
<td>-0.0189**</td>
<td>-0.0123</td>
</tr>
<tr>
<td>BDE-154</td>
<td>&lt;LOD</td>
<td>ref.</td>
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88
Abbreviation: TSH, thyroid-stimulating hormone; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; PTC, papillary thyroid cancer; ACEM, average causal mediation effect; ADE, average direct effect; 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; BB-153, 2,2’,4,4’,5,5’-hexabromobiphenyl; LOD: limit of detection; BMI, body mass index.
Hierarchical linear model and generalized linear mixed-effects model, adjusted for all PBDE and PBB congeners, BMI, and branch of military service.
*P-value <0.05.
**P-value <0.01.
***P-value <0.001.
Supplementary Figure 1-1. Scatter plots of TSH against BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) with zoom in the lower concentration parts.
Supplementary Figure 1-2. Scatter plots of TT3 against BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) with zoom in the lower concentration parts.
Supplementary Figure 1-3. Scatter plots of TT4 against BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) with zoom in the lower concentration parts.
Supplementary Figure 1-4. Scatter plots of FT4 against BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) with zoom in the lower concentration parts.
Supplementary Figure 2-1. Estimated effects of natural log transformed BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) on natural log transformed serum levels of TSH using generalized additive models, adjusted for BMI and branch of military service, among PTC cases.
Supplementary Figure 2-2. Estimated effects of natural log transformed BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) on natural log transformed serum levels of TT3 using generalized additive models, adjusted for BMI and branch of military service, among PTC cases.
Supplementary Figure 2-3. Estimated effects of natural log transformed BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) on natural log transformed serum levels of TT4 using generalized additive models, adjusted for BMI and branch of military service, among PTC cases.
Supplementary Figure 2-4. Estimated effects of natural log transformed BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) on natural log transformed serum levels of FT4 using generalized additive models, adjusted for BMI and branch of military service, among PTC cases.
Supplementary Figure 3-1. Estimated effects of natural log transformed BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) on natural log transformed serum levels of TSH using generalized additive models, adjusted for BMI and branch of military service, among controls.
Supplementary Figure 3-2. Estimated effects of natural log transformed BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) on natural log transformed serum levels of TT3 using generalized additive models, adjusted for BMI and branch of military service, among controls.
Supplementary Figure 3-3. Estimated effects of natural log transformed BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) on natural log transformed serum levels of TT4 using generalized additive models, adjusted for BMI and branch of military service, among controls.
Supplementary Figure 3-4. Estimated effects of natural log transformed BDE-28 (A), BDE-47 (B), BDE-85 (C), BDE-99 (D), BDE-100 (E), BDE-153 (F), BDE-154 (G), and BB-153 (H) on natural log transformed serum levels of FT4 using generalized additive models, adjusted for BMI and branch of military service, among controls.
Genetic Polymorphisms in Phase I and Phase II Metabolism/Detoxification and Thyroid Hormone Metabolism Pathways, Polybrominated Diphenyl Ethers, Thyroid-Stimulating Hormones, and Risk of Papillary Thyroid Cancer

Abstract

Background: Increased risk of papillary thyroid cancer (PTC) has been linked to exposure to polybrominated diphenyl ethers (PBDEs) and reduced serum level of thyroid-stimulating hormone (TSH), but effect of genetic variation in genes coding for enzymes involved in metabolism of PBDEs and TSH on risk of PTC and whether this variation modifies the PBDEs and TSH related risk of thyroid carcinogenesis remain unclear.

Methods: Using data from a case-control study nested within the Department of Defense Serum Repository (DoDSR) cohort, we evaluated 238 single nucleotide variants (SNVs) in 27 candidate genes in phase I and phase II metabolism/detoxification and thyroid hormone metabolism pathways in 317 papillary thyroid cancer (PTC) cases and 311 controls. Conditional logistic regression was used to estimate the associations between genetic polymorphisms and risk of PTC. Linear trend of the polymorphic effect was tested using an additive conditional logistic regression model. Gene-environment interaction was tested by unconditional logistic regression to investigate if the magnitude of carcinogenic effect of BDE-28 and TSH on PTC differs depending on genetic polymorphisms.

Results: Genetic polymorphism of GSTP1 rs4147581 was associated with risk of PTC in women and for large tumor (>10 mm), while GSTP1 rs1138272 was associated with risk of papillary microcarcinoma (≤10 mm). All the associations were non-significant after FDR-adjustment for multiple comparisons. Significant interactions were observed between BDE-28 and CYP2E1 rs7092584 in women and DIO2 rs12885300 for large PTC. In addition, serum level of TSH
significantly interacted with *UGT1A* rs1875263 and *DIO2* rs12885300 in men, and with *UGT1A* rs2011404 for large PTC.

*Conclusions:* This study suggested that genetic polymorphisms in genes involved in phase I and phase II metabolism/detoxification and thyroid hormone metabolism pathways could modify the effects of BDE-28 and TSH on risk of PTC. The effect modification varied by gender and tumor size. More studies with prospective design and larger statistical power are warranted to confirm these findings and to further understand the underlying mechanisms of genetic polymorphisms and PBDEs/TSH related pathogenesis of PTC.

*Keywords:* genetic polymorphism, metabolism and detoxification pathway, PBDEs, thyroid-stimulating hormone, papillary thyroid cancer
Increased risk of papillary thyroid cancer (PTC) has been linked to exposure to polybrominated diphenyl ethers (PBDEs) [43-45, 140] and abnormal, especially reduced, serum level of thyroid-stimulating hormone (TSH) [64, 68] in previous epidemiological studies. However, effect of genetic variation in genes coding for enzymes involved in metabolism, regulation, or functional activation of PBDEs and TSH on risk of PTC and whether this variation modifies the PBDEs and TSH related risk of thyroid carcinogenesis are still unclear.

As a class of brominated flame retardants (BFRs) that is widely distributed in the environment, PBDEs has been shown to be susceptible to several metabolic processes, including phase I oxidation via cytochrome P450 (CYP) isozymes and phase II conjugation via glucuronidation and/or sulfation enzymes (e.g., glutathione S-transferases [GSTs], uridine 5′-diphosphogluconosyltransferases [UDPGTs], and sulfotransferases [SULTs]) [148]. In addition, exposure to PBDEs can induce the activity of major thyroid hormone metabolic enzymes, including CYP isozymes, UDPGTs, SULTs, and deiodinases, and then disrupt the metabolism and homeostasis of thyroid hormones [19]. Variants in genes involved in coding phase I and phase II metabolism/detoxification enzymes (e.g., CYP1A1, CYP2D6, CYP2E1, GSTM1, and GSTT1) have been suggested to be associated with risk of PTC in some epidemiological studies [46-49], but these findings are inconclusive and need to be confirmed in more populations [149, 150]. There is also some evidence of associations for risk of thyroid cancer with common variants in genes involved in regulation of thyroid hormones (e.g., FOXE1, NKX2-1, DIRC3, and NRG1) [111, 112]. Experimental studies observed upregulated expression of type 3 deiodinase (D3) gene (i.e., DIO3) and downregulated expression of type 2 deiodinase (D2) gene (i.e., DIO2) in human PTC tissue, indicating effects of deiodinases (i.e., D2 and D3) on tumor growth and aggressiveness [151, 152], but the role of deiodinases in initiation and promotion of PTC is still unstudied. Investigation of the effect modification of genetic variation on risk of PTC is yet limited. One nested case-control study examined the interactions of genetic variants in metabolism/detoxification pathways with
tobacco and alcohol use in relation to risk of PTC, and reported significant interactions between *CYP26B1* and cigarette smoking and between *UGT2B7* and alcohol consumption [50]. Another case-control study in children from the Chernobyl nuclear accident area found independent effects of genetic polymorphisms in *FOXE1* and dose of ionizing radiation on the risk of PTC [153]. However, the role of genetic polymorphisms in phase I and phase II metabolism/detoxification and thyroid hormone metabolism pathways in modifying the association between environmental chemicals, thyroid hormones, and risk of PTC remains poorly understood.

Investigation of variation in genes related to coding for enzymes involved in metabolism of PBDEs and thyroid hormones may provide a better understanding of the etiology of PTC. To test our hypothesis that genetic polymorphisms in phase I and phase II metabolism/detoxification and thyroid hormone metabolism pathways are associated with risk of PTC and these variants further modify the carcinogenic effects of PBDEs and TSH on PTC, we evaluated 238 single nucleotide variants (SNVs) in 27 candidate genes, using data from a case-control study nested within the Department of Defense Serum Repository (DoDSR) cohort [64, 140].

**Methods**

**Study population**

Details of the nested case-control study design have been described in previous publications [64, 140] and in the Aim 1. Briefly, 742 pairs of PTC cases diagnosed between 2000 and 2013 and non-cancer (except for non-melanoma skin cancer) controls were recruited from the US military personnel who had serum samples drawn during active duty and stored in the DoDSR. Cases and controls were individually matched by date of birth (±1 year), gender, race/ethnicity, and midpoint of dates of selected four samples drawn (±1 year). All study procedures were approved by the Uniformed Services University Institutional Review Board, the Walter Reed National Military Medical Center, the DoD Joint Pathology Center, and the Human Investigation Committee of Yale
University. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects research.

Laboratory analyses

DNA samples were prepared using combinations of the last two 0.5-mL (total 1 mL) sera. At first, the combined serum samples were processed to extract human DNA using the QIAamp DNA Mini Kit (QIAGEN; Hilden, Germany). The extracted DNA samples were then quantified through a spectrophotometer. Since the minimum DNA quantity required for genotyping is 200 ng, a whole-genome amplification (WGA) using the REPLI-g UltraFast Mini Kit (QIAGEN; Hilden, Germany) was performed to obtain sufficient DNA prior to genotyping. A minimum of 50 ng input DNA was set for the WGA reaction to obtain high quality WGA DNA, which yielded a total of 336 case-control pairs (45.3%) who had satisfied the minimal amount of DNA for WGA and were qualified for genotyping. The distributions of demographic characteristics and military services were comparable between the 336 genotyped case-control pairs and the rest of participants (Supplementary Table 1).

The prepared DNA samples were sent to the Yale Keck Biotechnology Resource Laboratory (Yale University; New Haven, CT) for genotyping, which was performed by employing the Infinium® Global Screening Array-24 (GSA-24) v2.0 platform (Illumina, Inc.; Madison, WI). A total of 656,725 SNVs were genotyped for each DNA sample. The genotyping was repeated among 5% of the DNA samples for internal quality control (QC). External QC samples were also included in each assay. The external QC samples used were DNA extracted from human buffy coat with DNA concentration similar to the analytic samples. After each assay, the internal QC samples were evaluated to determine the quality and precision of genotyping. SNVs with repeat errors were removed from the genotyping results datafile. Upon passing the evaluation of internal QC, the results of genotyping were compared with the external QC samples for further assurance of quality.
The overall consistency rate was greater than 99%. Among the 672 genotyped samples, only 628 (93.5%) had a call rate of 90% or greater. The 10% GenCall score of the 628 samples were all greater than 0.20, and no outliers have been identified by plotting the 10% GenCall score against the call rate. Thus, the 628 samples with a call rate of ≥90% were eligible to be included in the further statistical analyses.

A total of 24 genes coding for the phase I and phase II metabolism/detoxification enzymes involved in the metabolism of PBDEs/PBBs and thyroid hormones were identified through the Gene database of National Center for Biotechnology Information (NCBI), including CYP1A1, CYP1B1, CYP1A2, CYP2D6, CYP2E1, CYP3A4, CYP3A5, GSTP1, GSTM1, GSTT1, UGT1A1, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, SULT1A1, SULT1A3, SULT1B1, SULT1E1, and SULT2A1. The genes DIO1, DIO2, and DIO3 coding for deiodinases that regulate activity and metabolism of thyroid hormones were also identified and included. Among the 656,725 SNVs that have been genotyped, a total of 2,039 loci in the 27 candidate genes were identified through the SNV database of NCBI. The tagging SNVs with a minor allele frequency (MAF) ≥0.05 were eligible for statistical analyses. The call frequency and Hardy-Weinberg equilibrium (HWE) were also evaluated for each tagging SNV to determine the quality of genotyping. Acceptable threshold of SNV call frequency was set to be ≥95%. HWE was assessed among controls by performing the chi-squared test. SNVs with a p-value for HWE ≥10^{-5} were considered to be in HWE and were eligible for statistical analyses. At last, a total of 238 SNVs were included in the final statistical analyses to estimate their associations with risk of PTC and their effects of modifying the associations between serum concentration of a PBDE congener (i.e., BDE-28) [140], TSH level [64], and risk of PTC.

Statistical analyses
Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between genetic polymorphisms and risk of PTC. For each SNV that included in a regression model, effect of rare homozygote (double-variant) and heterozygote (single-variant) on the risk of PTC was compared with that of common homozygote, respectively. The collective effect of allelic variation was examined by comparing the sum of rare homozygote and heterozygote to common homozygote. Linear trend of the polymorphic effect was tested using an additive conditional logistic regression model that assigns a value of 0 to common homozygote, 1 to heterozygote, and 2 to rare homozygote.

Analysis of gene-environment interaction was performed to investigate if the magnitude of carcinogenic effect of BDE-28 and TSH on PTC differs depending on genetic polymorphisms. This analysis was completed by fitting unconditional logistic regression models that include SNVs, categorical serum levels of BDE-28 or TSH, and an interaction term between SNVs and BDE-28 or between SNVs and TSH, respectively [154]. A significant p-value for the interaction term suggests an existing of gene-environment interaction. For SNVs showing significant gene-environment interaction, the associations between BDE-28, TSH, and risk of PTC were estimated and reported among homozygous genotype and a combination of heterozygous and rare homozygous genotypes, respectively.

Both the conditional logistic regression and gene-environment interaction analyses were conducted among the entire genotyped population and also among subgroups stratified by gender, histologic subtype (classical PTC vs. follicular variant of PTC), and tumor size (≤10 vs. >10 mm), respectively. All models were adjusted for body mass index (BMI; <18.5, 18.5-24.9, 25-29.9, and 30 kg/m²) and branch of military service (army, air force, marines and coast guard, and navy). The gene-environment interaction models were also adjusted for age, gender, race/ethnicity, and date of
sample collection. Models testing gene-environment interaction with BDE-28 were further adjusted for other PBDE/PBB congeners (i.e., BDE-47, -85, -99, -100, -153, -154, and BB-153).

All tests were 2-sided with a priori significance level set to be 0.01. Analyses of genetic polymorphisms and risk of PTC were further corrected for multiple comparisons by adjusting the false discovery rate (FDR) [155]. The Bonferroni correction was not employed because it is too conservative. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc.; Cary, North Carolina) and R, version 3.6.3 (R Foundation, Vienna, Austria).

Results

Demographic characteristics and military service of the genotyped PTC cases (n=317) and controls (n=311) were presented in Table 1. Since cases were individual matched to controls in the parent nested case-control study [64, 140], distributions of age, gender, and race/ethnicity were similar between cases and controls. BMI was also similar distributed between cases and controls, although nearly half of participants had missing BMI data (43.9% for cases and 42.4% for controls). PTC cases were more likely to have served in the Army (45.1% vs. 35.1%) or Air Force (23.3% vs. 18.7%) at the time of diagnosis, whereas controls were more likely to have served in the Navy (23.0% vs. 34.4%) or Marines/Coast Guard (8.5% vs. 11.9%) (P=0.0023).

Risk of PTC was suggested to be associated with DIO2 rs225014 (P_trend=0.026), SULT1B1 rs11569731 (P_trend=0.036), and GSTP1 rs4147581 (P_trend=0.050) (Table 2). The heterozygote of CYP1A2 rs2472304 was associated with an elevated risk of PTC (OR=1.88, 95% CI: 1.20, 2.97; P=0.0063), but this SNV was failed to meet the a priori significance level of 0.01 in the additive model (data not shown). A complete list of raw and FDR-adjusted P-values for linear trend of all 238 SNVs was available in the Supplementary Table 2. None of the associations remained significant after controlling for multiple comparisons.
Results from the subgroup analyses showed significant association between PTC risk and GSTP1 rs4147581 in women (OR=2.78, 95% CI: 1.27, 6.08 for rare homozygote; P\_trend=0.0082) (Supplementary Table 3) and for large tumor (>10 mm) (OR=2.35, 95% CI: 1.25, 4.42 for rare homozygote; P\_trend=0.0085) (Supplementary Table 5). GSTP1 rs1138272 was significantly associated with risk of microcarcinoma (≤10 mm) (OR=3.69, 95% CI: 1.46, 9.33 for rare homozygote; P\_trend=0.0045). But all these SNVs were no longer significant after FDR adjustment (data not shown). The heterozygous or the rare homozygous genotypes of UGT1A10/UGT1A8/UGT1A9 rs17864684, CYP1A2 rs2472304, and DIO2 rs225014 yielded statistically significant ORs in women, while the heterozygous genotypes of CYP1A2 rs2472304 and CYP2E1 rs6413419 yielded statistically significant ORs for large tumor. However, all these SNVs did not meet the significance level in the additive model (data not shown). No significant associations were observed for neither classical nor follicular variant of PTC (Supplementary Table 4).

Risk of classical PTC in relation to serum concentration of BDE-28 and serum level of TSH among the genotyped cases and controls were displayed in the Supplementary Table 6. The associations in genotyped population were similar to those in the entire study population for both men and women [64, 140]. The gene-environment interaction analysis for BDE-28 yielded a total of 7 SNVs with P\_interaction<0.05 (Table 3). Among the 7 SNVs, 3 were associated with UGT1Ax gene family (i.e., rs12995772, rs12469671, and rs1817154), while the other 4 were associated with CYP1A1 (rs1048943), CYP1A2 (rs762551), DIO1 (rs2268181), and DIO2 (rs7145153), respectively. No SNVs reached the a priori significance level of 0.01. When stratified the analysis by gender, only one SNV (rs7092584) in CYP2E1 showed statistically significant effect modification with BDE-28 on the risk of PTC in women (P\_interaction=0.0036) (Supplementary Table 8). Exposure to BDE-28 was associated with an increased risk of PTC in women who carrying minor allele (OR=9.69, 95%
CI: 0.47, 199.25) as compared to those who with common homozygous genotype (OR=0.89, 95% CI: 0.36, 2.17). The sub-analysis in large tumors also yielded one SNV (rs12885300) in DIO2 with $P_{interaction}=0.0076$ (Supplementary Table 11). The minor allele carriers were less likely to develop BDE-28 related large PTC (OR=0.44, 95% CI: 0.18, 1.10) as compared to the common homozygote carriers (OR=2.22, 95% CI: 0.78, 6.33). None of the SNVs met the significance level of 0.01 when the analyses were restricted in men (Supplementary Table 7), classical PTC (Supplementary Table 9), or microcarcinoma (Supplementary Table 10). Results from the sub-analysis for follicular variation of PTC were not shown due to small numbers.

Interactions between genetic variants and serum level of TSH on PTC risk were identified for 8 SNVs at a significance level of 0.05, but no SNVs at the a priori significance level of 0.01 (Table 4). Of the 8 SNVs with $P_{interaction}<0.05$, 3 were associated with CYP2E1 (i.e., rs2249694, rs743534, and rs2515641), 3 were associated with UGT1Ax gene family (i.e., rs2011404, rs17862847, and rs35203651), while the others were associated with GSTP1 (rs1138272) and DIO2 (rs12885300), respectively. Results from the subgroup analysis demonstrated statistically significant interaction with rs1875263 in UGT1Ax gene family ($P_{interaction}=0.0038$) and rs12885300 in DIO2 ($P_{interaction}=0.0074$) in men (Supplementary Table 12). Increased risk of PTC was associated with a lower level of TSH in men who carrying the common homozygous genotype of rs1875263 (OR=3.23, 95% CI: 1.24, 8.46), and with a higher level of TSH in men who carrying the common homozygous genotype of rs12885300 (OR=2.35, 95% CI: 1.03, 5.36). When the analysis was restricted in cases with large PTC, a statistically significant interaction was observed for rs2011404 in UGT1Ax gene family ($P_{interaction}=0.0075$) (Supplementary Table 16). For participants carrying minor allele, risk of large PTC was inversely associated with TSH level (OR=2.63, 95% CI: 0.79, 8.75 for lower level vs. OR=0.52, 95% CI: 0.15, 1.78 for higher level), but no association was observed for those who carrying the common homozygous genotype. None of the SNVs reached the significance level of 0.01 for women (Supplementary Table 13), classical PTC (Supplementary
Table 14), or microcarcinoma (Supplementary Table 15). Results from the sub-analysis for follicular variation of PTC were not shown due to limited numbers.

Discussion

In this study using data from a case-control study nested within the DoDSR cohort, we found that genetic polymorphism of *GSTP1* rs4147581 was associated with risk of PTC in women and for large tumor (>10 mm), while *GSTP1* rs1138272 was associated with risk of papillary microcarcinoma (≤10 mm). However, all these associations became non-significant after FDR-adjustment for multiple comparisons. Results from this study also suggested significant interactions between BDE-28 and *CYP2E1* rs7092584 in women and *DIO2* rs12885300 for large PTC. In addition, serum level of TSH significantly interacted with rs1875263 in *UGT1Ax* gene family and rs12885300 in *DIO2* among men, and with rs2011404 in *UGT1Ax* gene family for large PTC.

Previous candidate gene studies did not reach a consensus on the association between risk of PTC and genetic variants in genes coding phase I and phase II metabolism/detoxification enzymes, which are the key enzymes involved in metabolism of endobiotics (e.g., TSH and thyroid hormones) and detoxification of xenobiotics (e.g., PBDEs) [46-50, 149, 150]. Several genes in the phase I pathway, including *CYP1A1*, *CYP2D6*, and *CYP2E1*, were reported to be significantly associated with risk of PTC/differentiated thyroid cancer (DTC) in the Middle Eastern and the European populations [46, 47, 49]. However, two studies in the US population did not find any significant associations with CYP genes after correction for the multiple comparisons [50, 149]. In the phase II pathway, one study in the Caucasian Portuguese population suggested that *GSTM1* and *GSTT1* could weakly modify risk of PTC [48], while another study in the Korean population did not find any significant association between *GSTM1/GSTT1* and PTC susceptibility [150]. Our study in the US military personnel only observed suggestive associations with *GSTP1* in the servicewomen and by tumor size of PTC (Ptrend<0.01), but none of these associations remained significant after FDR-
adjustment for multiple comparisons. To minimize the potential population heterogeneity, we also examined the associations restricted in the Whites, accounting for ~61% of all the genotyped participants. No significant SNVs were identified either before or after FDR-adjustment (data not shown).

Results from this study did not support our hypothesis that genes involved in regulation of thyroid hormones (e.g., DIO1, DIO2, and DIO3) could modify the susceptibility of PTC. Although polymorphisms of DIO genes have been suggested to be associated with the thyroid hormone negative feedback regulation of TSH secretion [156, 157] and some benign thyroid diseases, such as autoimmune hypothyroidism [158], grave’s disease [159], and maternal thyroid dysfunction [160], evidence of DIO genes in developing thyroid cancer is still scanty. One case-control study investigated the association between four genetic variants (one in DIO1 and three in DIO2) and risk of DTC in the Saudi Arab population, and reported non-significant results [161]. More studies on the polymorphisms of DIO genes and susceptibility of thyroid cancer are need to clarify the role of DIO genes in thyroid carcinogenesis.

This study is the first to examine the interaction between genetic polymorphisms and PBDEs in risk of PTC. Our results indicated interactions between BDE-28 and CYP2E1 in women a priori significance level of 0.01. Exposure to PBDEs was reported to be associated with an enhanced expression of CYP2E1 [162]. Since CYP2E1 enzyme metabolizes many endogenous and exogenous substrates, it may be involved in varied pathways and processes of carcinogenesis, such as head and neck cancer [163], respiratory system cancer [164], and bladder cancer [165].

DIO2 was also observed to significantly interact with both BDE-28 for large tumors and with TSH in servicemen (P_{Interaction}<0.01). Exposure to PBDEs has been reported to decrease activity of DIO2 [166]. The D2 protein encoded by DIO2 gene is the key enzyme that converts T4 to bioactive T3.
The decreased activity of \textit{DIO2} could cause a reduced conversion rate from T4 to T3, which in turn leads to a decrease in TSH secretion, because TSH secretion is a negative function of serum T4 level. Thus, genetic polymorphisms of \textit{DIO2} gene may modify a mediation effect of TSH on the association between exposure to PBDEs and risk of developing PTC. This pathway is warranted to be further investigated in future mechanistic studies.

This study also found significantly interactions between serum level of TSH and two SNVs in \textit{UGT1Ax} gene family among servicemen and for large PTC (P_{interaction}<0.01), respectively. The \textit{UGT1A} genes encode several UDPGTs, which are responsible for the formation of glucuronides from a large variety of cytotoxic and genotoxic compounds, including carcinogens and reactive oxygen species [167]. \textit{UGT1A} polymorphisms have been associated with levothyroxine (LT4) dose required for suppression of TSH secretion in DTC patients [168]. Mediated by the E3 ubiquitin ligases WSB-1 and/or TEB4, ubiquitination by T4 binding to and/or T4 catalysis triggers D2 inactivation is an important step to regulate the activity of D2 [169]. Thus, \textit{UGT1A} polymorphisms may also influence the activity of D2, thereby triggering an alteration in TSH level [161], which is suggested to increase risk of PTC [64].

Strengths of this study include a relatively large number of male cases. Since women are approximately three times more likely to develop thyroid cancer than men, this provides sufficient statistical power to investigate and compare the effect of genetic polymorphisms by gender. The study population was composed entirely of the US active-duty military personnel, a younger population represents the age groups at which PTC risk is at its highest. Also, the heterogeneity in genetic predisposition of PTC could be minimized in this study population. The single-payer universal (i.e., equal access) military healthcare system minimizes potential selection bias from differences in access to medical care. Additionally, the serum concentrations of BDE-28 and TSH were prospectively assessed and were not influenced by the disease process or treatment.
Several limitations merit further consideration. There was a high percentage of participants with missing BMI data, which may have led to insufficient adjustment for BMI. Previous evidence has suggested lower prevalence of obesity and larger lean body mass of military personnel than the US civilian population [69], indicating less variation of BMI among the US military personnel. Thus, any effect of under-adjustment for BMI would likely be minimized in this study population. Furthermore, the stratified and gene-environment interaction analyses may have yielded unstable results due to the small subgroup counts. It is also possible that the findings for gene-environment interaction at a priori significance level of 0.01 were observed by chance due to the multiple comparisons. Future studies in general populations with increased statistical power are warranted to confirm our findings.

In conclusion, this study suggested that genetic polymorphisms in several genes involved in phase I and phase II metabolism/detoxification and thyroid hormone metabolism pathways could modify the effects of exposure to PBDEs and alternation in serum TSH level on risk of PTC. The effect modification varied by gender and tumor size. This exploratory study provides novel evidence to understand the underlying mechanisms of genetic polymorphisms and PBDEs/TSH related pathogenesis of PTC. More studies with prospective design and larger statistical power are merited to confirm these findings and to further understand the basis of the molecular biology behind them.
Acknowledgments

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Conflict of interest

The authors declare they have no actual or potential conflict of interests.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Uniformed Services University of the Health Sciences, the Department of Defense, or the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the Department of Defense, the CDC, the Public Health Service, or the US Department of Health and Human Services.
Table 1. Distributions of selected characteristics among genotyped PTC cases and controls.

<table>
<thead>
<tr>
<th>Age at diagnosis (year)</th>
<th>Cases (n=317)</th>
<th>Controls (n=311)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>96 (30.3)</td>
<td>91 (29.3)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>123 (38.8)</td>
<td>123 (39.6)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>79 (24.9)</td>
<td>79 (25.4)</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>19 (6.0)</td>
<td>18 (5.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Gender</td>
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</tr>
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<td>Male</td>
<td>168 (53.0)</td>
<td>168 (54.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>149 (47.0)</td>
<td>143 (46.0)</td>
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</tr>
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<td>Race/Ethnicity</td>
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<td></td>
</tr>
<tr>
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<td>189 (60.8)</td>
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<tr>
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<td>56 (18.0)</td>
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<td>123 (39.6)</td>
<td></td>
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<tr>
<td>25-29.9</td>
<td>58 (18.3)</td>
<td>51 (16.4)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>9 (2.8)</td>
<td>5 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
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<td>132 (42.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>Service</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Army</td>
<td>143 (45.1)</td>
<td>109 (35.1)</td>
<td></td>
</tr>
<tr>
<td>Air Force</td>
<td>74 (23.3)</td>
<td>58 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Marines and Coast Guard combined</td>
<td>27 (8.5)</td>
<td>37 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Navy</td>
<td>73 (23.0)</td>
<td>107 (34.4)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Histologic subtype</td>
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<td></td>
</tr>
<tr>
<td>Classical PTC</td>
<td>265 (83.6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Follicular variation of PTC</td>
<td>52 (16.4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>104 (32.8)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>196 (61.8)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>17 (5.4)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated by the Chi-squared test.
Table 2. Association between genotypes and risk of PTC at \( P_{trend} \leq 0.05 \).

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene/Region</th>
<th>SNV</th>
<th>Genotype</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>P-value</th>
</tr>
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<tbody>
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<td>14</td>
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<td>112</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>TC</td>
<td>155</td>
<td>129</td>
<td>1.16 (0.80-1.68)</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>34</td>
<td>67</td>
<td>0.36 (0.20-0.65)</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P for trend</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC+CC</td>
<td>189</td>
<td>196</td>
<td>0.90 (0.64-1.27)</td>
<td>0.54</td>
</tr>
<tr>
<td>4</td>
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<td>286</td>
<td>265</td>
<td>1.00</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>AG</td>
<td>30</td>
<td>44</td>
<td>0.59 (0.34-1.02)</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td>0</td>
<td>1</td>
<td>-</td>
<td>-</td>
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<td>P for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG+GG</td>
<td>30</td>
<td>45</td>
<td>0.57 (0.33-0.98)</td>
<td>0.044</td>
</tr>
<tr>
<td>11</td>
<td>GSTP1</td>
<td>rs4147581</td>
<td>GG</td>
<td>101</td>
<td>123</td>
<td>1.00</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CG</td>
<td>156</td>
<td>144</td>
<td>1.38 (0.92-2.08)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
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<td>44</td>
<td>1.68 (0.98-2.89)</td>
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</tr>
<tr>
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<td>P for trend</td>
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<td></td>
<td></td>
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<td>CG+CC</td>
<td>216</td>
<td>188</td>
<td>1.45 (0.97-2.15)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

Abbreviations: PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.
*Conditional logistic regression adjusted for BMI (<18.5, 18.5-24.9, 25-29.9, and 30 kg/m2) and branch of military service (army, air force, marines and coast guard, and navy).
Table 3. Effect modification of genotypes between serum concentration of BDE-28 (ng/g) and risk of PTC at $P_{\text{interaction}}$<0.05.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>&lt;LOD</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>≥LOD</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>CYP1A1</td>
<td>rs1048943</td>
<td>TT</td>
<td>191</td>
<td>182</td>
<td>1.00</td>
<td>87</td>
<td>86</td>
<td>1.02 (0.60-1.72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TG+GG</td>
<td>26</td>
<td>19</td>
<td>1.00</td>
<td>11</td>
<td>21</td>
<td>0.09 (0.01-0.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P for interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>1</td>
<td>DIO1</td>
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<td>TT</td>
<td>152</td>
<td>154</td>
<td>1.00</td>
<td>71</td>
<td>68</td>
<td>1.05 (0.59-1.89)</td>
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<tr>
<td></td>
<td></td>
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<td>TC+CC</td>
<td>65</td>
<td>47</td>
<td>1.00</td>
<td>27</td>
<td>39</td>
<td>0.39 (0.14-1.06)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>P for interaction</td>
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<td></td>
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<td>0.017</td>
</tr>
<tr>
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<td>UGT1A10, UGT1A8</td>
<td>rs12995772</td>
<td>CC</td>
<td>199</td>
<td>176</td>
<td>1.00</td>
<td>90</td>
<td>97</td>
<td>0.78 (0.46-1.32)</td>
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<tr>
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<td>18</td>
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<td>1.00</td>
<td>8</td>
<td>10</td>
<td>1.60 (0.17-14.96)</td>
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<td>0.83 (0.40-1.75)</td>
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<td>133</td>
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<td>80</td>
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<td>AA</td>
<td>135</td>
<td>128</td>
<td>1.00</td>
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<td>82</td>
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Abbreviations: BDE-28, 2,4,4'-tribromodiphenyl ether; PTC, papillary thyroid cancer; LOD: limit of detection; SNV, single nucleotide variant; OR, odds ratio; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, branch of military service, and other PBDE and PBB congeners.
Table 4. Effect modification of genotypes between serum level of TSH (μU/mL) and risk of PTC at Pinteraction<0.05.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>TSH ≤1.22</th>
<th>1.23-2.02</th>
<th>TSH ≥2.03</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
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<tr>
<td>14</td>
<td>DIO2</td>
<td>rs12885300</td>
<td>CC</td>
<td>71</td>
<td>64</td>
<td>1.51 (0.88-2.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC+TT</td>
<td>67</td>
<td>36</td>
<td>1.63 (0.91-2.93)</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
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<td>rs2011404</td>
<td>CC</td>
<td>99</td>
<td>85</td>
<td>1.32 (0.85-2.04)</td>
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<td></td>
<td></td>
<td></td>
<td>TC+TT</td>
<td>39</td>
<td>15</td>
<td>2.51 (1.01-6.20)</td>
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</tr>
<tr>
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<td>CYP2E1</td>
<td>rs2249694</td>
<td>GG</td>
<td>71</td>
<td>36</td>
<td>2.67 (1.50-4.77)</td>
</tr>
<tr>
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<td>AG+AA</td>
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<td>64</td>
<td>0.95 (0.55-1.64)</td>
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<td>11</td>
<td>GSTP1</td>
<td>rs1138272</td>
<td>CC</td>
<td>114</td>
<td>94</td>
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<td></td>
<td>TC+TT</td>
<td>24</td>
<td>6</td>
<td>6.91 (1.53-31.26)</td>
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<td></td>
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<td>rs17862847</td>
<td>TT</td>
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<td>79</td>
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<td></td>
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<td>TA+AA</td>
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<td>1.16 (0.51-2.61)</td>
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<td><strong>P for interaction</strong></td>
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<td></td>
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<td>CYP2E1</td>
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<td>AA</td>
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<td>50</td>
<td>2.06 (1.24-3.41)</td>
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<td>AC+CC</td>
<td>48</td>
<td>50</td>
<td>0.92 (0.48-1.74)</td>
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</tr>
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<td>rs35203651</td>
<td>TT</td>
<td>123</td>
<td>85</td>
<td>1.72 (1.12-2.62)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>TC+CC</td>
<td>15</td>
<td>15</td>
<td>0.77 (0.24-2.46)</td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td>CYP2E1</td>
<td>rs2515641</td>
<td>CC</td>
<td>89</td>
<td>50</td>
<td>2.04 (1.23-3.38)</td>
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<td></td>
<td></td>
<td></td>
<td>TC+TT</td>
<td>49</td>
<td>50</td>
<td>0.93 (0.49-1.77)</td>
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<tr>
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<td></td>
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<td><strong>P for interaction</strong></td>
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<td></td>
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</table>

Abbreviations: TSH, thyroid stimulating hormone; PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, and branch of military service.
Supplementary Table 1. Distributions of demographics among participants with and without genotyping.

<table>
<thead>
<tr>
<th></th>
<th>Genotyping (n=672)</th>
<th>Non-genotyping (n=812)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
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<td><strong>Age at diagnosis (year)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>35.2 (8.5)</td>
<td>35.1 (7.7)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
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</tr>
<tr>
<td>Male</td>
<td>360 (53.6)</td>
<td>442 (54.4)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>312 (46.4)</td>
<td>370 (45.6)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
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<td></td>
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<tr>
<td>White</td>
<td>412 (61.3)</td>
<td>523 (64.4)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>124 (18.5)</td>
<td>139 (17.1)</td>
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<td>Hispanic</td>
<td>70 (10.4)</td>
<td>66 (8.1)</td>
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</tr>
<tr>
<td>Other</td>
<td>52 (7.7)</td>
<td>58 (7.1)</td>
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<tr>
<td>Unknown</td>
<td>14 (2.1)</td>
<td>26 (3.2)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
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<tr>
<td>&lt;25</td>
<td>254 (37.8)</td>
<td>288 (35.5)</td>
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<tr>
<td>25-29.9</td>
<td>115 (17.1)</td>
<td>162 (20.0)</td>
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<td>≥30</td>
<td>14 (2.1)</td>
<td>12 (1.5)</td>
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<tr>
<td>Missing</td>
<td>289 (43.0)</td>
<td>350 (43.1)</td>
<td>0.41</td>
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<td><strong>Service</strong></td>
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<tr>
<td>Army</td>
<td>254 (37.8)</td>
<td>298 (36.7)</td>
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<tr>
<td>Air Force</td>
<td>154 (22.9)</td>
<td>189 (23.3)</td>
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<tr>
<td>Marines and Coast Guard combined</td>
<td>72 (10.7)</td>
<td>83 (10.2)</td>
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<tr>
<td>Navy</td>
<td>192 (28.6)</td>
<td>242 (29.8)</td>
<td>0.94</td>
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</table>

Abbreviations: SD, standard deviation; BMI, body mass index.

*Estimated by the Student's t-test for continuous variables or the Chi-squared test for categorical variables.
Supplementary Table 2. Raw and FDR-adjusted p-values for linear trend of 238 tagging SNVs.

<table>
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<tr>
<th>SNV</th>
<th>Gene/Region</th>
<th>Raw $P_{trend}$</th>
<th>FDR-adjusted $P_{trend}$</th>
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<td>$DIO2$</td>
<td>0.0256</td>
<td>0.9932</td>
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<td>rs11569731</td>
<td>$SULT1B1$</td>
<td>0.0359</td>
<td>0.9932</td>
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<td>rs4147581</td>
<td>$GSTP1$</td>
<td>0.0499</td>
<td>0.9932</td>
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<td>rs17862873</td>
<td>$UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A3$</td>
<td>0.0675</td>
<td>0.9932</td>
</tr>
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<td>$UGT1A10, UGT1A8$</td>
<td>0.0676</td>
<td>0.9932</td>
</tr>
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<td>rs17874938</td>
<td>$UGT1A8$</td>
<td>0.0702</td>
<td>0.9932</td>
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<td>rs28900371</td>
<td>$UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A3$</td>
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<td>0.9932</td>
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<td>0.9932</td>
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<td>0.0784</td>
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<td>0.9932</td>
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<td>0.0896</td>
<td>0.9932</td>
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<td>rs7145153</td>
<td>$DIO2$</td>
<td>0.0926</td>
<td>0.9932</td>
</tr>
<tr>
<td>rs17864690</td>
<td>$UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A9$</td>
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<td>0.9932</td>
</tr>
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<td>rs</td>
<td>Gene(s)</td>
<td>D1</td>
<td>D2</td>
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<td>0.9932</td>
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<td>SULT1B1</td>
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<td>0.9932</td>
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<td>0.9932</td>
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<td>0.9932</td>
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<td>0.2082</td>
<td>0.9932</td>
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<td>CYP1B</td>
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<td>UGT1A8</td>
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<td>0.9932</td>
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<td>0.9932</td>
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<td>CYP2E1</td>
<td>0.2632</td>
<td>0.9932</td>
</tr>
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<td>rs1453322</td>
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<td>0.2639</td>
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<td>GSTM1</td>
<td>0.3173</td>
<td>0.9932</td>
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<td>0.9932</td>
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<tr>
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<td>SULT2A1</td>
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Abbreviations: FDR, false discovery rate; SNV, single nucleotide variant.

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<td>GG</td>
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</tr>
<tr>
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</tr>
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<td>24</td>
</tr>
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</tr>
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<td></td>
<td></td>
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<td>GC+GG</td>
<td>109</td>
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</tr>
</tbody>
</table>

Abbreviations: PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.

*Conditional logistic regression adjusted for BMI and branch of military service.
Supplementary Table 4. Association between genotypes and risk of PTC by histologic subtype.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>Classical PTC (n=510)</th>
<th>Follicular variant of PTC (n=100)</th>
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<tbody>
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<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
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<td>rs225014</td>
<td>TT</td>
<td>98</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC</td>
<td>132</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>29</td>
<td>49</td>
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<tr>
<td></td>
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<td>P for trend</td>
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</tr>
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</tr>
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<td>208</td>
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</tr>
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<td>GG</td>
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<td>1</td>
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<td></td>
<td></td>
<td>AG+GG</td>
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<td></td>
</tr>
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<td>GG</td>
<td>82</td>
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<td></td>
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<td>114</td>
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<td>CC</td>
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<td></td>
<td>P for trend</td>
<td></td>
</tr>
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<td></td>
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<td>CG+CC</td>
<td>183</td>
<td>149</td>
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</tbody>
</table>

Abbreviations: PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.

*Conditional logistic regression adjusted for BMI and branch of military service.
Supplementary Table 5. Association between genotypes and risk of PTC by tumor size.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>(\leq 10) mm (n=201)</th>
<th></th>
<th>(&gt;10) mm (n=378)</th>
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</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>14</td>
<td>DIO2</td>
<td>rs225014</td>
<td>TT</td>
<td>33</td>
<td>32</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC</td>
<td>61</td>
<td>39</td>
<td>1.61 (0.83-3.11)</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>9</td>
<td>24</td>
<td>0.37 (0.15-0.94)</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SULT1B1</td>
<td>rs11569731</td>
<td>AA</td>
<td>93</td>
<td>82</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG</td>
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<td>14</td>
<td>0.71 (0.29-1.72)</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
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<td>GG</td>
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<td>0</td>
<td>-</td>
<td>-</td>
</tr>
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<td></td>
<td></td>
<td>P for trend</td>
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<td></td>
<td>0.44</td>
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</tr>
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<td>GSTP1</td>
<td>rs4147581</td>
<td>GG</td>
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<td>36</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CG</td>
<td>51</td>
<td>47</td>
<td>1.05 (0.56-1.98)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>15</td>
<td>14</td>
<td>0.99 (0.41-2.38)</td>
<td>0.98</td>
</tr>
<tr>
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<td></td>
<td>P for trend</td>
<td></td>
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<tr>
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<td>GSTP1</td>
<td>rs1138272</td>
<td>CC</td>
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<td>90</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC</td>
<td>22</td>
<td>7</td>
<td>3.69 (1.46-9.33)</td>
<td>0.0058</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.0045</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC+TT</td>
<td>23</td>
<td>7</td>
<td>3.81 (1.51-9.59)</td>
<td>0.0045</td>
</tr>
</tbody>
</table>

Abbreviations: PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.

*Conditional logistic regression adjusted for BMI and branch of military service.
Supplementary Table 6. Risk of classical PTC associated with lipid-corrected serum concentration of BDE-28 and serum level of TSH among genotyped population, stratified by gender.

<table>
<thead>
<tr>
<th>BDE-28&lt;sup&gt;a&lt;/sup&gt; (ng/g)</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;LOD</td>
<td>97</td>
<td>98</td>
<td>1.00</td>
<td>86</td>
<td>92</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;LOD-1.56</td>
<td>17</td>
<td>13</td>
<td>1.32 (0.51-3.40)</td>
<td>9</td>
<td>14</td>
<td>0.65 (0.20-2.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.57-3.18</td>
<td>12</td>
<td>19</td>
<td>0.52 (0.20-1.36)</td>
<td>19</td>
<td>12</td>
<td>1.78 (0.48-6.58)</td>
<td></td>
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</tr>
<tr>
<td>3.19-80.10</td>
<td>20</td>
<td>17</td>
<td>1.27 (0.33-4.96)</td>
<td>18</td>
<td>13</td>
<td>1.73 (0.31-9.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td>0.56</td>
<td></td>
<td></td>
<td>0.25</td>
<td></td>
<td></td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>TSH&lt;sup&gt;b&lt;/sup&gt; (μU/ml)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;0.30</td>
<td>1</td>
<td>2</td>
<td>0.90 (0.05-15.39)</td>
<td>8</td>
<td>3</td>
<td>2.54 (0.43-15.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.30-1.19</td>
<td>35</td>
<td>50</td>
<td>1.27 (0.56-2.87)</td>
<td>29</td>
<td>53</td>
<td>0.49 (0.19-1.29)</td>
<td></td>
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</tr>
<tr>
<td>1.20-1.93</td>
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<td>57</td>
<td>1.00</td>
<td>25</td>
<td>48</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.94-4.20</td>
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<td>65</td>
<td>0.70 (0.30-1.63)</td>
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<td>44</td>
<td>0.15 (0.04-0.59)</td>
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</tr>
<tr>
<td>&gt;4.20</td>
<td>9</td>
<td>6</td>
<td>4.72 (0.82-27.27)</td>
<td>3</td>
<td>8</td>
<td>0.60 (0.06-5.76)</td>
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<td></td>
</tr>
<tr>
<td><strong>P for trend (within the normal range)</strong></td>
<td>0.18</td>
<td></td>
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<td>0.13</td>
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</tr>
<tr>
<td><strong>P for trend (overall)</strong></td>
<td>0.48</td>
<td></td>
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<td>0.088</td>
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<td>0.13</td>
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</tbody>
</table>

Abbreviations: PTC, papillary thyroid cancer; BDE-28, 2,4,4'-tribromodiphenyl ether; TSH, thyroid stimulating hormone; OR, odds ratio; LOD: limit of detection; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; BMI, body mass index.

<sup>a</sup> Multi-chemical conditional logistic regression, adjusted for all PBDE and PBB congeners, BMI, and branch of military service.

<sup>b</sup> Conditional logistic regression, adjusted for BMI and branch of military service.
Supplementary Table 7. Effect modification of genotypes between serum concentration of BDE-28 (ng/g) and risk of PTC in men at $P_{\text{interaction}}$<0.05.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>Cases &lt;LOD</th>
<th>Controls &lt;LOD</th>
<th>OR* (95% CI)</th>
<th>Cases ≥LOD</th>
<th>Controls ≥LOD</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
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<td>rs1817154</td>
<td>AA</td>
<td>73</td>
<td>68</td>
<td>1.00</td>
<td>34</td>
<td>31</td>
<td>0.89 (0.37-2.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AC+CC</td>
<td>45</td>
<td>39</td>
<td>1.00</td>
<td>15</td>
<td>30</td>
<td>0.36 (0.12-1.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P_{\text{for interaction}}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>DIO1</td>
<td>rs2235544</td>
<td>CC</td>
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<td>26</td>
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<td>18</td>
<td>0.31 (0.06-1.47)</td>
</tr>
<tr>
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<td>81</td>
<td>1.00</td>
<td>37</td>
<td>43</td>
<td>0.75 (0.35-1.58)</td>
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<tr>
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<td>$P_{\text{for interaction}}$</td>
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</tr>
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<td>50</td>
<td>0.37 (0.17-0.82)</td>
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<td>$P_{\text{for interaction}}$</td>
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<td>1.00</td>
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<td>57</td>
<td>0.55 (0.28-1.09)</td>
</tr>
<tr>
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<td></td>
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<td>AC+AA</td>
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<td>14</td>
<td>1.00</td>
<td>1</td>
<td>4</td>
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</tr>
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<td>$P_{\text{for interaction}}$</td>
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</tr>
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<td>75</td>
<td>69</td>
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<td>43</td>
<td>38</td>
<td>1.00</td>
<td>10</td>
<td>24</td>
<td>0.37 (0.10-1.42)</td>
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<td>$P_{\text{for interaction}}$</td>
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<td>0.68 (0.30-1.52)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>TC+TT</td>
<td>43</td>
<td>38</td>
<td>1.00</td>
<td>10</td>
<td>24</td>
<td>0.37 (0.10-1.42)</td>
</tr>
<tr>
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<td>$P_{\text{for interaction}}$</td>
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<td>68</td>
<td>1.00</td>
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<td>37</td>
<td>0.68 (0.31-1.52)</td>
</tr>
<tr>
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<td></td>
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<td>TA+TT</td>
<td>43</td>
<td>39</td>
<td>1.00</td>
<td>10</td>
<td>24</td>
<td>0.37 (0.10-1.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P_{\text{for interaction}}$</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: BDE-28, 2,4,4'-tribromodiphenyl ether; PTC, papillary thyroid cancer; LOD: limit of detection; SNV, single nucleotide variant; OR, odds ratio; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, branch of military service, and other PBDE and PBB congeners.
Supplementary Table 8. Effect modification of genotypes between serum concentration of BDE-28 (ng/g) and risk of PTC in women at $P_{\text{interaction}}<0.05$.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>Cases &lt;LOD</th>
<th>Controls &lt;LOD</th>
<th>OR* (95% CI)</th>
<th>Cases ≥LOD</th>
<th>Controls ≥LOD</th>
<th>OR* (95% CI)</th>
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</thead>
<tbody>
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<td>10</td>
<td>CYP2E1</td>
<td>rs7092584</td>
<td>CC</td>
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<td>67</td>
<td>1.00</td>
<td>34</td>
<td>37</td>
<td>0.89 (0.36-2.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC+TT</td>
<td>19</td>
<td>27</td>
<td>1.00</td>
<td>15</td>
<td>9</td>
<td>9.69 (0.47-199.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P_{\text{for interaction}}$</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>CYP2E1</td>
<td>rs3813867</td>
<td>GG</td>
<td>91</td>
<td>89</td>
<td>1.00</td>
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Abbreviations: BDE-28, 2,4,4'-tribromodiphenyl ether; PTC, papillary thyroid cancer; LOD: limit of detection; SNV, single nucleotide variant; OR, odds ratio; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, branch of military service, and other PBDE and PBB congeners.
Supplementary Table 9. Effect modification of genotypes between serum concentration of BDE-28 (ng/g) and risk of classical PTC at $P_{\text{interaction}}<0.05$.

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*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, branch of military service, and other PBDE and PBB congeners.

Abbreviations: BDE-28, 2,4,4'-tribromodiphenyl ether; PTC, papillary thyroid cancer; LOD, limit of detection; SNV, single nucleotide variant; OR, odds ratio; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; BMI, body mass index.
Supplementary Table 10. Effect modification of genotypes between serum concentration of BDE-28 (ng/g) and risk of papillary microcarcinoma (≤10 mm) at $P_{\text{interaction}}<0.05$.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>Cases &lt;LOD</th>
<th>Controls OR* (95% CI)</th>
<th>Cases ≥LOD</th>
<th>Controls OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
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<td>rs2547238</td>
<td>GG</td>
<td>34</td>
<td>37 1.00</td>
<td>17</td>
<td>20 1.67 (0.46-6.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GC+CC</td>
<td>39</td>
<td>20 1.00</td>
<td>13</td>
<td>17 0.20 (0.03-1.37)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>$P_{\text{for interaction}}$</td>
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</tr>
<tr>
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<td>GG</td>
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<td>15</td>
<td>17 0.98 (0.29-3.37)</td>
</tr>
<tr>
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<td></td>
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<td>32</td>
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<td>15</td>
<td>20 0.09 (0.01-0.85)</td>
</tr>
<tr>
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<td>$P_{\text{for interaction}}$</td>
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<td>CC</td>
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<td>30 0.73 (0.19-2.79)</td>
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<td>25 1.00</td>
<td>10</td>
<td>7 5.48 (0.60-50.31)</td>
</tr>
<tr>
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<td>$P_{\text{for interaction}}$</td>
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<td>rs6731242</td>
<td>TT</td>
<td>51</td>
<td>43 1.00</td>
<td>20</td>
<td>24 0.99 (0.33-2.93)</td>
</tr>
<tr>
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<td>TG+GG</td>
<td>22</td>
<td>14 1.00</td>
<td>10</td>
<td>13 0.01 (&lt;0.001-1.83)</td>
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<tr>
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<td>30 0.59 (0.15-2.31)</td>
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<td>TC+TT</td>
<td>33</td>
<td>23 1.00</td>
<td>10</td>
<td>7 4.62 (0.54-39.68)</td>
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<td>$P_{\text{for interaction}}$</td>
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<td>TT</td>
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<td>28 0.71 (0.26-1.93)</td>
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<tr>
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<td></td>
<td></td>
<td>TG+GG</td>
<td>12</td>
<td>9 1.00</td>
<td>2</td>
<td>9 10.65 (&lt;0.001-&gt;9999.99)</td>
</tr>
<tr>
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<td>CC</td>
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<td>17</td>
<td>15 1.50 (0.43-5.18)</td>
</tr>
<tr>
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<td>TC+TT</td>
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<td>13</td>
<td>22 0.07 (0.01-0.86)</td>
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<td>11</td>
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<td>28 1.00</td>
<td>19</td>
<td>14 0.38 (0.10-1.54)</td>
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<td>AA</td>
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<td>49 1.00</td>
<td>25</td>
<td>24 0.81 (0.29-2.27)</td>
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</table>

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, branch of military service, and other PBDE and PBB congeners.*

**Abbreviations:** BDE-28, 2,4,4'-tribromodiphenyl ether; LOD: limit of detection; SNV, single nucleotide variant; OR, odds ratio; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; BMI, body mass index.
Supplementary Table 11. Effect modification of genotypes between serum concentration of BDE-28 (ng/g) and risk of large PTC (>10 mm) at $P_{\text{interaction}}$<0.05.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>&lt;LOD Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>≥LOD Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>$P_{\text{for interaction}}$</th>
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</thead>
<tbody>
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<td>rs12885300</td>
<td>CC</td>
<td>65</td>
<td>71</td>
<td>1.00</td>
<td>34</td>
<td>23</td>
<td>2.22 (0.78-6.33)</td>
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<tr>
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<td>64</td>
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<td>1.00</td>
<td>32</td>
<td>41</td>
<td>0.44 (0.18-1.10)</td>
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</tr>
<tr>
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<td>DIO1</td>
<td>rs2268181</td>
<td>TT</td>
<td>95</td>
<td>91</td>
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<td>49</td>
<td>38</td>
<td>1.47 (0.68-3.19)</td>
<td>0.016</td>
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<td>TC+CC</td>
<td>34</td>
<td>27</td>
<td>1.00</td>
<td>17</td>
<td>26</td>
<td>0.28 (0.06-1.28)</td>
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</tr>
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<td>51</td>
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<td>41</td>
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<td>0.61 (0.25-1.49)</td>
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<td>77</td>
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<td>25</td>
<td>35</td>
<td>2.32 (0.76-7.09)</td>
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</tr>
<tr>
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<td>TT</td>
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<td>111</td>
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<td>57</td>
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<td>1.38 (0.68-2.80)</td>
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</tr>
<tr>
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<td>TG+GG</td>
<td>12</td>
<td>7</td>
<td>1.00</td>
<td>9</td>
<td>12</td>
<td>0.88 (0.44-2.10)</td>
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</tr>
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<td>2</td>
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<td>50</td>
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<td>27</td>
<td>0.55 (0.18-1.67)</td>
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</tr>
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<td>rs2294512</td>
<td>GG</td>
<td>64</td>
<td>43</td>
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<td>0.68 (0.24-1.99)</td>
<td>0.038</td>
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<td>1.00</td>
<td>39</td>
<td>31</td>
<td>1.27 (0.53-3.08)</td>
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<td>CC</td>
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<td>104</td>
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<td>61</td>
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<td>0.88 (0.44-1.77)</td>
<td>0.047</td>
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<td>AC+AA</td>
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<td>1.00</td>
<td>5</td>
<td>7</td>
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</tbody>
</table>

Abbreviations: BDE-28, 2,4,4’-tribromodiphenyl ether; PTC, papillary thyroid cancer; LOD: limit of detection; SNV, single nucleotide variant; OR, odds ratio; PBED, polybrominated diphenyl ether; PBB, polybrominated biphenyl; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, branch of military service, and other PBDE and PBB congeners.
**Supplementary Table 12. Effect modification of genotypes between serum level of TSH (μU/mL) and risk of PTC in men at P_{interaction}<0.05.**

<table>
<thead>
<tr>
<th>Chromosome</th>
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<th>SNV</th>
<th>Genotype</th>
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<th>1.23-2.02</th>
<th>≥2.03</th>
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<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
<td>Cases</td>
</tr>
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<td>CC</td>
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<td>13</td>
<td>3.23 (1.24-8.46)</td>
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<tr>
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<td></td>
<td></td>
<td>TC+TT</td>
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<td>36</td>
<td>1.22 (0.58-2.57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P for interaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>DIO2</td>
<td>rs12885300</td>
<td>CC</td>
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<td>19</td>
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<tr>
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<td>P for interaction</td>
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<td></td>
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<td>GG</td>
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<td>1.53 (0.70-3.33)</td>
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<td>P for interaction</td>
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<td>35</td>
<td>1.53 (0.70-3.33)</td>
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<td></td>
<td>TC+TT</td>
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<td>31</td>
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<td>P for interaction</td>
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<td><strong>TT</strong></td>
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<td>14</td>
<td>2.83 (1.10-7.27)</td>
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<tr>
<td>-------</td>
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<td><strong>TC+TT</strong></td>
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<td>18</td>
<td></td>
<td>2.31 (0.91-5.85)</td>
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<tr>
<td></td>
<td></td>
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<td>Controls</td>
<td>OR (95% CI)</td>
</tr>
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Abbreviations: TSH, thyroid stimulating hormone; PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, and branch of military service.
## Supplementary Table 13. Effect modification of genotypes between serum level of TSH (μU/mL) and risk of PTC in women at $P_{\text{interaction}}<0.05$.

<table>
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<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>$\leq1.22$</th>
<th>1.23-2.02</th>
<th>$\geq2.03$</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
</tr>
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<td>rs1875263</td>
<td>CC</td>
<td>18</td>
<td>19</td>
<td>0.60 (0.20-1.77)</td>
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<td></td>
<td></td>
<td></td>
<td>TC+TT</td>
<td>54</td>
<td>32</td>
<td>2.41 (1.19-4.89)</td>
</tr>
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<td></td>
<td><strong>P for interaction</strong></td>
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</tr>
<tr>
<td>19</td>
<td>SULT2A1</td>
<td>rs2547238</td>
<td>GG</td>
<td>50</td>
<td>25</td>
<td>2.78 (1.28-6.03)</td>
</tr>
<tr>
<td></td>
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<td>GC+CC</td>
<td>22</td>
<td>26</td>
<td>0.64 (0.25-1.65)</td>
</tr>
<tr>
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<td>CC</td>
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<td>55</td>
<td>29</td>
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<td>CC</td>
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<td>39</td>
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<td>1.54 (0.65-3.66)</td>
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<td>AA</td>
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<td>AG+GG</td>
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<td>GSTP1</td>
<td>rs36211089</td>
<td>CC</td>
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<td>22</td>
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<td>TC+TT</td>
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<td><strong>P for interaction</strong></td>
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Abbreviations: TSH, thyroid stimulating hormone; PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, and branch of military service.
Supplementary Table 14. Effect modification of genotypes between serum level of TSH (μU/mL) and risk of classical PTC at $P_{\text{interaction}}$<0.05.

<table>
<thead>
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<th>Chromosome</th>
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<th>SNV</th>
<th>Genotype</th>
<th>≤1.22 Cases</th>
<th>≥1.23-2.02 Cases</th>
<th>≥2.03 Cases</th>
<th>OR* (95% CI)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
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<td>38</td>
<td>38</td>
<td>1.44 (0.77-2.69)</td>
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<td>43</td>
<td>1.00</td>
<td>54</td>
<td>43</td>
<td>0.41 (0.21-0.78)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>TC+TT</td>
<td>52</td>
<td>48</td>
<td>30</td>
<td>1.10 (0.56-2.14)</td>
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<td>CC</td>
<td>89</td>
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<td>57</td>
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<td>76</td>
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<td>GG</td>
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<td>36</td>
<td>1.68 (0.95-2.99)</td>
<td>45</td>
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<td>1.00</td>
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</table>

Abbreviations: TSH, thyroid stimulating hormone; PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, and branch of military service.
Supplementary Table 15. Effect modification of genotypes between serum level of TSH (μU/mL) and risk of papillary microcarcinoma (≤10 mm) at P_{interaction}<0.05.

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<th>Genotype</th>
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<td></td>
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<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
<td>Cases</td>
</tr>
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<td>CYP2E1</td>
<td>rs6413423</td>
<td>TT</td>
<td>43</td>
<td>21</td>
<td>2.17 (0.98-4.84)</td>
<td>28</td>
<td>31</td>
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<td>26</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>TG+GG</td>
<td>2</td>
<td>6</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>1.00</td>
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<tr>
<td>19</td>
<td>SULT2A1</td>
<td>rs296365</td>
<td>CC</td>
<td>21</td>
<td>10</td>
<td>2.78 (0.71-10.94)</td>
<td>16</td>
<td>12</td>
<td>1.00</td>
<td>10</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CG+GG</td>
<td>24</td>
<td>17</td>
<td>2.66 (0.89-7.91)</td>
<td>14</td>
<td>22</td>
<td>1.00</td>
<td>19</td>
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<tr>
<td>14</td>
<td>DIO2</td>
<td>rs12885300</td>
<td>CC</td>
<td>20</td>
<td>17</td>
<td>1.44 (0.50-4.18)</td>
<td>15</td>
<td>20</td>
<td>1.00</td>
<td>16</td>
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<td></td>
<td></td>
<td></td>
<td>TC+TT</td>
<td>25</td>
<td>10</td>
<td>2.36 (0.76-7.37)</td>
<td>15</td>
<td>14</td>
<td>1.00</td>
<td>13</td>
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</tbody>
</table>

Abbreviations: TSH, thyroid stimulating hormone; PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index.

*Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, and branch of military service.
Supplementary Table 15. Effect modification of genotypes between serum level of TSH (μU/mL) and risk of large PTC (>10 mm) at $P_{interaction}<$0.05.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>SNV</th>
<th>Genotype</th>
<th>≤1.22</th>
<th>1.23-2.02</th>
<th>≥2.03</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR* (95% CI)</td>
<td>Cases</td>
</tr>
<tr>
<td>2</td>
<td>UGT1A10, UGT1A8, UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4</td>
<td>rs2011404</td>
<td>C</td>
<td>57</td>
<td>55</td>
<td>1.06 (0.60-1.87)</td>
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<td>TC+TT</td>
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<td>7</td>
<td>2.63 (0.79-8.75)</td>
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<td>P for interaction</td>
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<td>0.0075</td>
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<td>SULT2A1</td>
<td>rs2547238</td>
<td>GG</td>
<td>57</td>
<td>31</td>
<td>1.85 (0.97-3.56)</td>
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<td></td>
<td></td>
<td>GC+CC</td>
<td>28</td>
<td>31</td>
<td>0.84 (0.36-1.96)</td>
</tr>
<tr>
<td>P for interaction</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
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<td>rs17862847</td>
<td>TT</td>
<td>64</td>
<td>51</td>
<td>1.60 (0.89-2.90)</td>
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<td>0.87 (0.29-2.60)</td>
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<td>P for interaction</td>
<td></td>
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<td></td>
<td>0.036</td>
</tr>
</tbody>
</table>

Abbreviations: TSH, thyroid stimulating hormone; PTC, papillary thyroid cancer; SNV, single nucleotide variant; OR, odds ratio; BMI, body mass index. *Unconditional logistic regression adjusted for age, gender, race/ethnicity, date of serum sample collection, BMI, and branch of military service.
CONCLUSION

This study used data from a nested case-control study including 742 pairs of cases diagnosed with papillary thyroid cancer (PTC) and individually matched controls with pre-diagnostic serum concentrations of polybrominated diphenyl ethers (PBDEs), as well as serum levels of thyroid-stimulating hormone (TSH) and thyroid hormones, from the Department of Defense Serum Repository (DoDSR). We tested the hypothesis that exposure to elevated PBDEs increases the risk of PTC and the increased risk posed by PBDEs is through the disruption of thyroid hormones. We also investigated the effects of genetic polymorphisms in genes involved in metabolism/detoxification of PBDEs and thyroid hormones on the association between PBDEs, thyroid hormones, and risk of PTC.

Results from this study suggested that exposure to PBDEs (i.e., BDE-28) and dysregulate serum levels of TSH were associated with increased risk of PTC. We found that increasing serum levels of BDE-28 were associated with an elevated risk of classical PTC. The association between BDE-28 and risk of classical PTC was mainly observed for cases with large tumors (tumor size >10 mm), and was stronger among women. Serum TSH level below the normal range (<0.3 μU/ml) was associated with an elevated risk of PTC among women, while TSH level above the normal range (>4.2 μU/ml) was associated with an increased risk of PTC among men. There was an inverse association between PTC risk and TSH level within the normal range (0.3-4.2 μU/ml) among men and women. The observed associations between serum level of TSH and risk of PTC varied by histological subtype (classical vs. follicular variant PTCs) and by tumor size (≤10 vs. >10 mm) among both genders.

This study also found relationships between PBDE/polybrominated biphenyl (PBB) congeners and serum levels of TSH and thyroid hormones. We observed significantly nonmonotonic relationships
between serum concentrations of BDE-153 and BB-153 and serum levels of TT3 and TT4 in PTC cases, and between BDE-47, -100, and -153 in relation to FT4 level in controls. The associations between PBDEs/PBBs and serum levels of TSH and thyroid hormones were stronger in cases than those in controls. Among cases, higher serum concentrations of BDE-153 and BB-153 were associated with increased level of TSH and decreased levels of TT3 and TT4, while higher concentration of BDE-100 was associated with reduced level of TSH and elevated level of TT4. When stratified by gender, the effects of BDE-100 on levels of TSH and TT4 were only observed among men, while the effects of BDE-153 and BB-153 on levels of TT3 and TT4 were only observed among women. However, results from the causal mediation analysis did not support our hypothesis that the thyroid carcinogenesis of PBDEs/PBBs is mainly operated through disruption of thyroid hormone homeostasis and fluctuation of TSH level.

Investigation on the genetic polymorphisms and gene-environment interactions in genes involved in phase I and phase II metabolism/detoxification and thyroid hormone metabolism pathways identified several genes that could modify the effects of exposure to BDE-28 and alternation in serum TSH level on risk of PTC. Results suggested significant interactions between BDE-28 and \textit{CYP2E1} rs7092584 in women and \textit{DIO2} rs12885300 for large PTC (tumor size >10 mm) at \textit{a priori} significance level of 0.01. In addition, serum level of TSH significantly interacted with rs1875263 in \textit{UGT1A} gene and rs12885300 in \textit{DIO2} gene among men, and with rs2011404 in \textit{UGT1A} gene for large PTC.

Further investigation into the association between BDE-28, other PBDE/PBB congeners, alternatives of brominated flame retardants (BFRs), and PTC risk is warranted among different populations to confirm our findings and identify high risk populations who are susceptible to these chemicals. More studies using multiple longitudinal measurements are also warranted to further understand mechanisms underlying the endocrine disrupting effect of PBDEs/PBBs. Future studies
with prospective design and larger statistical power are also merited to confirm our findings on the gene-environment interactions in other populations and to explore the underlying mechanisms of genetic polymorphisms and PBDEs/TSH related pathogenesis of PTC.

Findings of this study provides valuable evidence to the link between exposure to PBDEs and risk of PTC, which will promote further regulations on production and application of PBDEs. Since serum level of TSH has been improved to be associated with risk of PTC, there could be significant clinical implications to monitor and regulate thyroid hormone levels among the most susceptible populations, such as patients with abnormal thyroid functions and those with benign thyroid disease or thyroidectomy, to mitigate the risk of thyroid carcinogenesis. Results from the gene-environment interaction analysis provide novel evidence to understand the basis of the molecular biology behind the initiation and promotion of PTC. With further understanding the pathogenesis of PTC, as well as implementing appropriate regulation and intervention, it should be pursued to decrease the incidence of PTC in the public, and to reduce the health and economic burdens caused by thyroid cancer.
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