Exposure to Flame Retardant Chemicals and Occurrence and Severity of Papillary Thyroid Cancer: A Case-Control Study

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Short Title: Flame Retardant Chemicals and Thyroid Cancer

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Highlights:

- Exposure to flame retardants was measured for PTC patients and matched controls.
- PTC patients had higher levels of some flame retardants in their homes.
- Associations with FRs varied based on tumor aggressiveness and mutation status.

Key Words: Flame Retardant Chemicals; BDE-209; tris(2-chloroethyl) phosphate (TCEP); Papillary Thyroid Cancer; BRAF V600E

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Abstract:

Background: Thyroid cancer is the fastest increasing cancer in the U.S., and papillary thyroid cancer (PTC) accounts for >90% of incident cases. Increasing exposure to flame retardant chemicals (FRs) has raised concerns about their possible role in this 'epidemic'. The current study was designed to test the hypothesis that higher exposure to FRs is associated with increased odds of PTC.

Methods: PTC patients at the Duke Cancer Institute were approached and invited to participate. Age- and gender-matched controls were recruited from the Duke Health System and surrounding communities. Because suitable biomarkers of long-term exposure do not exist for many common FRs, and levels of FRs in dust are significantly correlated with exposure, relationships between FRs in household dust and PTC were evaluated in addition to available biomarkers. PTC status, measures of aggressiveness (e.g. tumor size) and BRAF V600E mutation were included as outcomes.

Results: Higher levels of some FRs, particularly decabromodiphenyl ether (BDE-209) and tris(2-chloroethyl) phosphate in dust, were associated with increased odds of PTC. Participants with dust BDE-209 concentrations above the median level were 2.29 times as likely to have PTC [95% confidence interval: 1.03, 5.08] compared to those with low BDE-209 concentrations. Associations varied based on tumor aggressiveness and mutation status; TCEP was more strongly associated with larger, more aggressive tumors and BDE-209 was associated with smaller, less aggressive tumors.

Conclusions: Taken together, these results suggest exposure to FRs in the home, particularly BDE-209 and TCEP, may be associated with PTC occurrence and severity, and warrant further study.

1. Introduction

The incidence of thyroid cancer has dramatically increased world-wide over the last several decades (Ho et al. 2015). In the United States, thyroid cancer incidence has increased by an average of 3% per year over the last four decades, making thyroid cancer one of the fastest increasing cancer among both American women and men (Chen et al. 2009; Lim et al. 2017). This observation has been almost exclusively the result of an epidemic of papillary thyroid cancer (PTC), which now comprises approximately 84% of new cases (Lim et al. 2017). While radiation exposure, family history, and obesity are established risk factors, little research has investigated the role of other environmental exposures, which may be significant contributors to increasing PTC incidence (Kitahara and Sosa 2016).

Use of flame retardants (FRs) also increased over the last several decades due to the implementation of mandatory and voluntary flammability standards for furniture, electronics, and construction materials (Alaee et al. 2003; van der Veen and de Boer 2012). Polybrominated diphenyl ethers (PBDEs) were once among the most commonly used FRs in consumer products; they were routinely applied to furniture (Penta-BDE commercial mixture) and electronics (Deca-BDE mixture). However, their persistence in the environment, high bio-accumulation potential, and possible toxicity led to their phase-out in many regions of the world beginning in the early-2000s (Fromme et al. 2016). Since that time, industry has turned to various alternatives to meet flammability standards, including alternate brominated FRs and organophosphate FRs (PFR) (Stapleton et al. 2012b; van der Veen and de Boer 2012).

These types of FRs are not chemically bound to the products in which they are used, leaving them predisposed to leach into the environment and resulting in widespread human exposure, particularly in home environments. They are ubiquitously detected in indoor dust

samples, which is thought to be a primary source of exposure in the United States (e.g. (Lorber 2008; Stapleton et al. 2009; Watkins et al. 2013; Xu et al. 2016)); numerous studies have shown that levels of FRs in household dust are strongly correlated with biomarkers of exposure, and the Environmental Protection Agency estimates that 80% of the population's exposure to PBDE flame retardants is from indoor dust (Hoffman et al. 2014; Hoffman et al. 2015; Johnson et al. 2010; Lorber 2008; Stapleton et al. 2012a). Recent work suggests that although the levels of exposure to some FRs (e.g. Penta-BDE constituents) may be declining, human exposure to other FRs (e.g. PFRs) is likely increasing (Hoffman et al. 2017). This is particularly concerning, as emerging literature suggests that exposure to FRs is likely to impact human health (Allen et al. 2016; Meeker et al. 2013; Oulhote et al. 2016; Preston et al. 2017).

PBDEs share a similar chemical structure with thyroid hormones, and as such, they have received considerable attention with respect to their impact on thyroid regulation and clinically significant thyroid disease (Allen et al. 2016; Oulhote et al. 2016; Zhao et al. 2015). Although much less is known about the potential impact of other FRs, PFRs have been associated with alterations in thyroid hormone concentrations in some (Kim et al. 2015; Meeker and Stapleton 2010; Meeker et al. 2013; Preston et al. 2017; Wang et al. 2013; Xu et al. 2015) but not all studies (Moser et al. 2015).

Thyroid disease is associated with the growth of some cancers and has been linked to the prevalence of several types of cancer, including thyroid, suggesting that chemicals that disrupt thyroid hormone homeostasis in a significant way could contribute to cancer risk or severity (e.g. Lin et al. 2016; Hellevik et al. 2009; D'Avanzo et al. 2005; Brinton et al. 2007; Søgaard et al 2016; Moeller and Führer 2013). Given the relationship reported between FR exposures and thyroid hormone regulation, we hypothesize that exposure to FRs could increase cancer risk, and

in particular thyroid cancer risk. Indeed, many FRs are considered carcinogens and have been associated with the increased development of hepatocellular adenomas and carcinomas in chronically exposed rodents. In separate studies, rats exposed to Deca-BDE and TCEP experienced increased rates of thyroid gland follicular cell adenomas and carcinomas (NTP 1991; NTP 1986).

Despite animal evidence indicating that the thyroid may be particularly sensitive to FRs, the impact of FR exposure on human thyroid cancer risk remains unknown, particularly for the newer-use PFRs and alternative BFRs. To our knowledge, only one study has investigated this potential association; Aschebrook-Kilfoy et al. (2015) reported no association between exposure to Penta-BDEs and PTC (Aschebrook-Kilfoy et al. 2015), but other FRs, including BDE-209 and the newer use FRs, were not investigated. Therefore, the current study was designed to test the hypothesis that higher exposure to FRs in the home environment is associated with increased odds of PTC. To accomplish this, a matched case-control study design was used. Traditional biomarkers of PBDE exposure (i.e. serum PBDE levels) were employed; since suitable biomarkers of long-term exposure do not exist for many other common FRs, relationships between FRs in household dust and PTC also were evaluated. This represents the first study to investigate relationships between PTC and many commonly used FRs detected in the home environment.

2. Subjects and Methods

2.1 Study Participants

All study protocols were reviewed and approved by the Duke University Health System Institutional Review Board. Between April 2014 and January 2016, patients newly diagnosed

with PTC and referred to endocrinology or endocrine surgery at the Duke Cancer Institute or Duke University Hospital were approached and invited to participate in the study by their treating physician. Willing participants then were contacted by our study team and enrolled. Control participants were recruited as described below and were matched to enrolled cases based on sex and age (within seven years of the cases' age at enrollment). Other Duke patients undergoing routine wellness care or care for unrelated medical issues were randomly selected and invited to participate as control participants. Flyers were placed in Duke University medical facilities as a means of recruiting additional control participants. Supplemental Figure 1 provides additional detail on participant recruitment and study component completion; for several matched pairs, only dust or blood samples were available for both the case and control. Paired blood and household dust samples were used for 92 participants, and other participants contributed either blood or household dust samples.

2.1.1. Inclusion and exclusion criteria

To reduce potential selection bias, inclusion was restricted to individuals living within 50 miles of Duke. To confirm that levels of exposure in the current home were reflective of exposure occurring over the last several years (e.g. before the diagnosis of PTC was established), inclusion was restricted to individuals that had lived in the same home for at least two years. Because a supplemental goal of our larger research effort was to evaluate the impact of FR exposure on thyroid function, pregnant women were excluded, as thyroid hormone levels vary considerably during pregnancy (Alemu et al. 2016). Inclusion of controls was restricted to individuals with no history of thyroid cancer or disease (current thyroid status was verified with biochemical testing).

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117 2.2. Clinical assessment

118 Clinical and pathologic information for the cases was obtained during a detailed review
119 of each PTC case's medical records, including the size of the primary tumor, focality of tumors
120 within the thyroid gland (uni- or multi-focal), status of cervical lymph nodes (nodal metastases
121 present/absent) and distant metastases (present/absent), extra-thyroidal extension
122 (present/absent), and the American Joint Committee on Cancer (AJCC) pathologic stage
123 (tumor/node/metastasis, or TNM) 7th edition (Edge et al. 2010). These variables were generally
124 dichotomized for statistical analyses based on the distribution of data among cases. For example,
125 tumor size was classified as "small" for tumors less than 2 cm and "large" for tumors larger than
126 2 cm. In addition, BRAF V600E mutation status (+/-) was assessed for a subset of cases (n=45).
127 The BRAF V600E mutation (+) is common among PTCs and has been associated overall with
128 more aggressive tumors; therefore, it may serve as an indicator of patient prognosis (Xing et al.
129 2013). Investigating relationships between exposure and BRAF mutations could provide
130 information about a potential mechanism by which FRs impact PTC occurrence.

131

132 2.3. FRs in household dust

133 Upon enrollment, study personnel visited each participant's home to obtain environmental
134 samples (e.g. household dust) and conduct study questionnaires. Participants were instructed not
135 to vacuum their home for at least two days prior to their study visit. During the visit, the main
136 living area of the home was vacuumed using a Eureka Mighty Might vacuum with a cellulose
137 thimble fitted in the hose attachment to collect the dust, similar to collection methods used in our

previous studies (Stapleton et al. 2012a). Dust samples were wrapped in aluminum foil and immediately frozen upon collection.

Compounds assessed in dust included Penta-BDE constituents (i.e. BDE-47, BDE-99, BDE-100, BDE-153, and BDE-154), Deca-BDE (i.e. BDE-209), several commonly used PFRs [i.e. triphenyl phosphate (TPHP), tris(1,3-dichloroisopropyl)phosphate (TDCIPP), tris(1-chloro-2-isopropyl)phosphate (TCIPP), and tris(2-chloroethyl) phosphate (TCEP)], and two alternative brominated flame retardants [2-ethylhexyl-2,3,4,5 tetrabromobenzoate (TBB or EH-TBB) and bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate (TBPH or BEH-TEBP)]. Dust samples were assessed for these compounds using previously published methods (Hoffman et al. 2015; Stapleton et al. 2012; Stapleton et al. 2014); briefly, samples (about 100 mg) were spiked with the following internal standards: d15-TDCIPP (154.8 ng), 13C-TPHP (100 ng), 13C-EH-TBB (100 ng), 13C-BEH-TEBP (100 ng), FBDE-69 (30.0 ng), and 13C BDE-209 (30.0 ng). The dust was extracted with 50:50 dichloromethane/hexane (v/v) via sonication extraction three times and then concentrated to 1.0 mL using a nitrogen evaporator system. These extracts were cleaned using Florisil solid-phase extraction (Supelclean ENVI-Florisil, 6 mL, 500 mg bed weight; Supelco), eluting the F1 fraction with 10 6 mL hexane (brominated compounds) and the F2 fraction with 10 mL ethyl acetate (PFRs). Each fraction was concentrated to about 1 mL and then transferred to an autosampler vial for analysis by GC/MS. Brominated flame retardants were quantified using GC/MS operated in electron capture negative ionization mode (GC/ECNI-MS), whereas the organophosphate flame retardants were quantified using GC/MS in electron impact mode (GC/EI-MS). Due to co-elution issues with BDE-99 and EH-TBB, extracts were also run on GC/EI-MS to quantify BDE-99 alone (monitoring the [M]+ and [M-Br]+ fragments). Recovery of the internal standards was assessed using 13C-CDE141 for FBDE-69 and 13C

BDE-209, d9-tris(2-chloroethyl) phosphate (d9-TCEP; 227 ng) for d15-TDCIPP, and d15-triphenyl phosphate (d15-TPHP; 128 ng) for 13C-TPHP. Recoveries of FBDE-69, 13C-BDE-209, d15-TDCIPP, and 13C-TPHP were on average 75, 70, 97, and 106%, respectively. Standard Reference Material (SRM) 2585 (National Institute of Standards & Technology, Gaithersburg, MD) was used to ensure accuracy and ranged from 73 to 111% relative to the certified values.

2.4. Serum PBDEs

All study participants were asked to provide non-fasting blood samples in which PBDEs were measured. Serum samples were assessed for 27 PBDEs as described in Butt et al. 2016. Briefly, serum samples were spiked with 2.5 ng of FBDE-69. Samples were sonicated with 2.0 mL 0.1 M formic acid and 6.0 mL water to denature serum proteins. Following conditioning of the column with 5.0 mL dichloromethane, methanol, and water each, the samples were loaded on a Waters Oasis HLB column (500 mg bed weight, 6 mL) and washed with 5.0 mL water. PBDE analytes were eluted with 10.0 mL of 1:1 dichloromethane/ethyl acetate (v/v) then concentrated to near dryness using a nitrogen evaporator and reconstituted in 1.0 mL hexane. These samples were further cleaned using a silica column cartridge (1 g, Waters, Sep-Pak), eluting the F1 fraction with 10.0 mL hexane for the PBDEs. The F1 fraction was concentrated to about 100 μL and spiked with 5.0 ng 13C-CDE-141 to assess recovery of FBDE-69 and 13C-BDE-209, respectively. This fraction was analyzed using GC/MS in electron capture negative ionization mode for twenty-seven PBDEs. Recoveries of FBDE-69 averaged 67%. Standard Reference Material (SRM) 1958 (National Institute of Standards & Technology, Gaithersburg, MD) was used to ensure accuracy. Measurements in SRM 1958 relative to the certified values were 129%

for BDE-47 and 75% for BDE-153.Statistical analyses were conducted for congeners detected in greater than 70% of serum samples. Because PBDEs can bind to lipids in serum, individual BDE measures were lipid-corrected prior to statistical analysis using measurements of total cholesterol and triglycerides (Covaci et al. 2006). Lipid measurement was conducted by LabCorp in Burlington, NC using standard protocols. However, analyses were also conducted with wet weight PBDE concentrations, and nearly identical results were obtained. To facilitate comparisons with other studies, we present serum concentrations and results from lipid corrected analyses.

2.5. Statistical analyses

Descriptive statistics were calculated to examine the detection and distribution of FRs in serum and household dust. Concentrations were log-normally distributed, and preliminary analyses suggested that associations between FRs and outcomes were unlikely to be linear. As such, non-parametric statistical analyses were used or levels of each FR were dichotomized at the median value among controls to represent 'high' and 'low' exposure in predictive models. Kruskal-Wallis tests were used to assess bivariate associations between FRs and PTC outcomes. Logistic regression models were used to examine associations between exposure and case status while controlling for potential confounding factors. Standard polytomous regression (i.e. multinomial regression) analyses were used to evaluate relationships between exposure and outcomes with multiple levels (tumor size, histopathology, etc.).

Regression analyses were adjusted for participant age and household income, which are variables hypothesized to be related to both FR exposures and thyroid cancer risk or diagnosis. Ten participants chose not to provide their household income; for these participants, income was

imputed as the average household income in the census tract in which they were living at the time of enrollment. Analyses were conducted including body mass index (BMI) as a covariate (categorical as in Table 1). However, it is possible that BMI may be on the causal pathway between FR exposure and PTC; therefore, analyses also were performed that excluded BMI. Results were nearly identical; thus, BMI-adjusted models are presented. In addition to these variables, race (white vs. non-white) and employment status (employed vs. unemployed) were considered to be potential confounders, but neither impacted effect estimates. Additionally, confounding by cigarette smoking was considered; current smoking was uncommon among participants (n=7 current smokers), and therefore it was not included in analyses. Participants were also asked about their past exposure to ionizing radiation. None reported significant prior exposure, and accordingly, radiation was not included in analyses.

Because FRs are highly correlated in both dust and serum (making it difficult to include multiple exposures in a single model), separate models were constructed for each FR while recognizing that exposures do not occur in isolation. Accordingly, principle component analyses were conducted to systematically assess FR mixtures. Results of these analyses did not provide any additional insights and are not shown.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina). Statistical significance was set at a $p < 0.05$ and we did not perform adjustment for multiple comparisons, as has been recommended in the epidemiologic literature (Rothman 1990).

3. Results

3.1. Study population

229 Reflecting known gender differences in PTC risk, our final study population was 78.6%
230 female (Table 1). The mean age of study participants was 48 years (among cases, 39% were <45
231 years of age, a threshold used in AJCC staging (Edge et al. 2010)). Cases and controls were
232 similar with respect to race and ethnicity, household income, and health history. Cases and
233 controls were also similar with respect to the number of years they reported living at the current
234 address, which was more than 10 years for both. Among PTC cases, the majority were AJCC
235 stage 1 (62.9%), and tumors were generally contained to the thyroid (70%; Table 1). The BRAF
236 V600E mutation was common; 62.2% of the 45 cases with BRAF V600E assessment were
237 positive for the mutation.
238
239 3.2. FRs in household dust
240 FRs were detected in all house dust samples, and concentrations spanned several orders
241 of magnitude, similar to other studies in the United States (Dodson et al. 2012; Hoffman et al.
242 2014; K. Hoffman et al. 2015; Stapleton et al. 2008; Stapleton et al. 2012a). As a chemical class,
243 PFRs were detected most frequently and in the highest concentrations (**Figure 1**). For example,
244 median TCIPP concentrations in household dust were over 2000 ng/g (i.e. parts per billion) for
245 both cases and controls, similar to what has been reported in the literature. As is frequently
246 observed, FRs in household dust were correlated (Supplemental Table 1). The highest
247 correlations were observed between PBDE congeners used in the PentaBDE FR mixture
248 (r_s=0.70-0.88) and between TBB and TBPH, which are both used in Firemaster® 550, a
249 commonly applied flame retardant mixture. Bivariate analyses demonstrated significant (i.e.
250 BDE 209 p=0.05), or near significant (i.e. TCEP p=0.13 and TPHP p=0.12) differences in the
251 median dust FR concentrations in the homes of cases and controls. After adjustment for potential

252 confounding by participant, household income, and body mass index, PTC cases were
253 significantly more likely to have high concentrations of TCEP and BDE-209 in their house dust
254 (Table 2). For example, those with dust BDE-209 levels above the median were 2.29 times as
255 likely to be cases compared to those with house dust levels below the median (95% Confidence
256 Interval [CI]: 1.03, 5.08, p=0.04). In addition, results were suggestive of an association between
257 higher dust TPHP concentrations and PTC, but these did not reach statistical significance (odds
258 ratio (OR)=2.07; 95% CI: 0.94, 4.56; p=0.07). The levels of other FRs in household dust were
259 not associated with the odds of PTC in bivariate or multivariate analyses.
260
261 3.3. Dust FRs and measures of tumor aggressiveness
262 FRs also were associated with markers of tumor aggressiveness (Table 3; results not
263 shown for bivariate analyses). For example, high levels of BDE-209 were only associated with
264 tumors contained in the thyroid, those that were pT1a or pT1b and pN0 (low stage indicating
265 tumor is less than 2 cm and has not spread to the lymph nodes), suggesting that BDE-209 may
266 contribute to the risk of smaller, less aggressive PTCs. Associations between TPHP and PTC
267 also were stronger for pT1a and pT1b tumors (tumors less than 2 cm). Conversely, higher levels
268 of TCEP were associated with extrathyroidal extension, more advanced T-stage, and nodal
269 metastasis. Of note, AJCC stage was considered as a potential outcome. Results tended to
270 suggest that BDE-209, TPHP, and TCEP all were associated with higher AJCC stage, potentially
271 as an artifact of residual confounding by age, which is inherently related to AJCC staging and
272 which was associated with FRs in this study. AJCC stage results are shown in Supplemental
273 Table 2.
274

3.4. Dust FRs and BRAF V600E mutation

Associations between FRs and PTC varied by the presence of the BRAF V600E mutation, with high exposure generally more strongly related to BRAF V600E(-) tumors (Table 4). For example, in adjusted analyses, participants with high levels of BDE-209 in house dust were 14.2 times as likely to be BRAF(-) cases compared to controls, although confidence intervals were quite wide (95% CI: 1.63, 123; p=0.02). Although other cases also were more likely to have high levels of BDE-209 in their homes, associations were not statistically significant for BRAF(+) cases or participants for whom BRAF was not assessed. A similar pattern was observed for TPHP, with stronger associations between exposure and BRAF(-) tumors. Although TCEP followed a similar pattern, with BRAF V600E(-) cancers more strongly linked with high exposure, results were not statistically significant in analysis where case status was stratified by the presence or absence of the BRAF V600E mutation.

3.5. Serum PBDE FRs

Of the 27 PBDEs measured in serum samples, only two were detected in more than 70% of serum samples, and spanning several orders of magnitude, similar to other studies (Sjodin et al. 2008). The median concentrations of BDE-47 and BDE-153 in serum were 9.9 and 5.0 ng/g lipid among controls, respectively, and 8.9 and 4.1 ng/g lipid among cases ($p>0.05$). BDE-47 in serum was significantly correlated with BDE-47 in dust ($r_s=0.35$, $p=0.004$), but no relationship between BDE-153 in dust and serum was observed. There was no evidence of association between serum BDE-47 and BDE-153 levels and PTC (Supplemental Table 2). Investigating more-detailed case definitions (e.g. presence of BRAF V600E mutation) did not provide additional insight (Supplemental Table 3).

4. Discussion

The incidence of PTC has increased over the past several decades, a period over which the use of FRs also increased. Our results from this case-control study support our original hypothesis and suggest that exposure to some FRs in the home environment (i.e. BDE-209 and TCEP) may be related to increased risk for the development of clinically significant PTC. To our knowledge, this is the first work to assess associations between PTC and exposure to PFRs, alternate BFRs, and Deca-BDE. In addition, this work investigated associations based on genetics/mutation status, which is a major strength of our study, and highlights a need to further investigate environment and gene interactions in cancer research. We observed the strongest association for Deca-BDE and BRAF negative tumors, suggesting an alternate mutation or mechanistic pathway between exposure and PTC.

While thyroid cancers of all sizes have been observed to increase in the United States over the last 30 years, smaller PTCs (<2 cm, and especially ≤1 cm) appear to have increased at the fastest rate (Chen et al. 2009). Chen et al. reported that between 1988 and 2005, incidence rates for tumors <1.0 cm increased by an average of 8.6 percent annually, while the incidence of tumors ≥4 cm increased at 5.7 percent per year (among women) (Chen et al. 2009). Many have suggested that this could be the result of surveillance bias based on increasing use of diagnostic imaging like ultrasound, CT, MRI, and PET scanning, resulting in the finding of more 'incidental' thyroid nodules that represent thyroid cancers that are subclinical (Chen et al. 2009; Ho et al. 2015; Kitahara and Sosa 2016). While there are certainly other potential explanations for observed incidence trends, our results suggest that exposure to BDE-209 in house dust may be associated with an increased risk for the development of these small PTCs. A similar pattern

was observed for TPHP, although this finding was not statistically significant. If BDE-209 is playing a significant role in the etiology of small PTCs, the incidence rate of these types of tumors would be expected to begin to decline in the coming decades due to the voluntary Deca-BDE phase-out. However, our results suggest that TPHP also might contribute to an increased risk for small PTCs, and data suggest that exposure to TPHP may have increased over the last decade (Hoffman et al. 2017). Perhaps of more concern, our results suggest that exposure to TCEP may be associated with increased risk of more aggressive PTCs.

A previous study investigated associations between serum biomarkers of Penta-BDEs and thyroid cancer, finding no associations (Aschebrook-Kilfoy et al. 2015). Similar to previous work, associations between Penta-BDE compounds in serum or household dust were not associated with PTC in our present work. However, other FRs, including BDE-209, were not investigated in the work of Aschebrook-Kilfoy et al. (2015). Using house dust as a measure of long-term chronic exposure may have many benefits over traditional approaches of using serum biomarkers, particularly as it allows for the measurement and detection of a wider range of FRs.

Our results should be interpreted in the context of several important limitations. Analyses largely relied on the levels of FRs in the home environment as a proxy for personal exposure. While this approach is likely to result in some misclassification because exposure in other environments is not captured (e.g. at work or in the car), it is an efficient means of assessing exposure to a wide range of FRs that occur in mixtures, particularly those for which long-term exposure biomarkers have not been validated. PFRs, for example, are rapidly metabolized and excreted in urine; therefore, assessing urinary concentrations at the time of diagnosis may not be reflective of past average/chronic exposures. Nonetheless, because sources of exposure to PFRs may be relatively constant over time, the collection of urine samples in

future studies could provide additional insights. Unfortunately, urine samples were not collected for the majority of participants in our current work. Household dust FR concentrations are thought to be correlated over the course of several years (Stapleton et al. 2014; Whitehead et al. 2013; Dodson et al. 2012) and are highly correlated with personal exposure (Bramwell 2016; Hoffman et al. 2014; Hoffman et al. 2015; Stapleton et al. 2012a). To ensure that dust measurements were reflective of exposure preceding diagnosis, study participation was restricted to individuals that had lived in their homes for a minimum of two years. However, participants lived in their homes for an average of more than10 years at the time of enrollment, suggesting that FR measures in dust likely reflect longer-term exposures, although we acknowledge that the latency period between exposure to FRs and the development of PTC could be substantially longer. A cohort study design with long-term follow-up would be better suited to address this issue; however, we are unaware of any cohort studies that are banking novel exposure markers, such as household dust. In addition, exposures to flame retardants occur in mixtures. Although we considered the use of PCA to assess the impacts of commonly occurring FR mixtures, our sample size limited our ability to assess the joint impact of multiple FRs simultaneously. Additionally assessing mixtures of FRs should be included as a goal of future studies with a sufficient sample size.

5. Conclusion

With the incidence of thyroid cancer quickly increasing and little knowledge of what may be leading to this drastic increase (outside of 'over diagnosis'), understanding potential environmental factors contributing to thyroid cancer is critical. Our results suggest that exposure to BDE-209 and TCEP in the home environment may be associated with an increased risk of PTC. This is a critical concern, particularly as the use of FRs is expected to increase in the future

(Green 2015). Given the increase in mortality associated with PTC (Lim et al. 2017) and the high financial demands placed upon thyroid patients for treatment and follow-up, more research is urgently needed to investigate these associations and determine if these trends are replicated in a larger cohort.

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505 **Table 1: Selected demographic and pathologic characteristics of 140 study participants.**

	Cases (n=70)		Controls (n=70)		
	Mean ± St. Dev. or n	**Range or %**	**Mean ± St. Dev. or n**	**Range or %**	**p-value**
Age (years)	48.6 ± 11.8	26-75	48.1 ± 11.8	28-80	0.8
Years in Current Home [a]	11.5 ± 10.8	2-69	10.9 ± 9.6	2-46	0.75
Sex					
Male	15	21.4	15	21.4	--
Female	55	78.6	55	78.6	
Race					
White	54	77.1	56	80.0	0.59
African American	10	14.3	11	15.7	
Other	6	8.6	3	4.3	
Ethnicity					
Non-Hispanic or Latino	66	94.3	69	98.6	0.21
Hispanic or Latino	4	5.7	1	1.4	
Annual Household Income [b]					
<$50,000	16	22.9	14	20.0	0.59
$50-100,000	24	34.3	20	28.6	
>$100,000	30	42.9	36	51.4	
History of Other Cancer	11	15.7	10	14.3	0.75
BMI					
Underweight or normal	42	60.0	37	52.9	0.39
Overweight or obese	28	40.0	33	47.1	
AJCC stage					
1	44	62.9	--	--	--
2, 3, or 4	23	32.9	--	--	
NA [c]	3	4.3	--	--	
T-Stage					
1a or 1b	36	51.4	--	--	--
2, 3, or 4	31	44.3	--	--	
NA [c]	3	4.3	--	--	
N-Stage					
0	31	44.3	--	--	--
1a or 1b	23	32.9	--	--	
X	13	18.6	--	--	
NA [c]	3	4.3	--	--	
BRAF V600E					
(+)	28	40.0	--	--	--
(-)	17	24.3	--	--	
not assessed [d]	25	35.7	--	--	
Extrathyroidal extension					
Present	17	24.3	--	--	--
Absent	49	70.0	--	--	
not available [c]	4	5.7	--	--	

506 [a] Residential duration information was missing for 7 participants. As a requirement for enrollment, it was verified
507 that all participants had lived in their current home at least 2 years.
508 [b] 10 participants chose not to provide income information. For these participants, income was imputed as the median
509 household income for their census tract.
510 [c] NA-not available, because the patient did not have surgery at Duke or information was not included in their Duke
511 medical record.
512 [d] BRAF V600E status was assessed for a subset of participants.

513 **Table 2:** Adjusted odds ratios for PTC for FR exposure above the median (n=116).

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Mixture	Individual FR	OR (95% CI), p-value
Alternate BFRs	TBB	0.62 (0.29, 1.31), p=0.21
	TBPH	1.22 (0.56, 2.65), p=0.61
PFRs	TPHP	2.07 (0.94, 4.56), p=0.07
	TDCIPP	1.49 (0.69, 3.20), p=0.31
	TCEP	2.42 (1.10, 5.33), p=0.03
	TCIPP	0.92 (0.43, 1.97), p=0.83
Penta-BDE	BDE-47	0.80 (0.38, 1.70), p=0.57
	BDE-99	0.75 (0.36, 1.59), p=0.45
	BDE-100	0.88 (0.42, 1.87), p=0.74
	BDE-153	0.77 (0.37, 1.63), p=0.50
	BDE-154	0.80 (0.38, 1.70), p=0.56
Deca-BDE	BDE-209	2.29 (1.03, 5.08), p=0.04

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534 **Table 3:** Adjusted odds ratios by indicator of tumor aggressiveness for FR exposure above the
535 median (n=108 for extra thyroidal extension and n=110 for T-stage and N-stage).

	Extra-thyroidal extension		T-stage		N-stage	
FR	**Present**	**OR (95% CI)**	**Stage**	**OR (95% CI)**	**Stage**	**OR (95% CI)**
TBB	No	0.72 (0.31, 1.64)	1a or 1b	0.52 (0.20, 1.34)	X	0.44 (0.10, 1.94)
	Yes	0.49 (0.14, 1.66)	2, 3 or 4	0.8 (0.31, 2.09)	0	0.59 (0.21, 1.60)
					1	0.79 (0.28, 2.21)
TBPH	No	1.28 (0.55, 3.00)	1a or 1b	1.29 (0.50, 3.31)	X	0.61 (0.15, 2.58)
	Yes	1.01 (0.31, 3.30)	2, 3 or 4	1.11 (0.42, 2.96)	0	0.97 (0.36, 2.66)
					1	2.04 (0.68, 6.18)
TPHP	No	2.11 (0.88, 5.04)	1a or 1b	3.63 (1.26, 10.4)*	X	4.81 (0.86, 27.0)
	Yes	2.03 (0.59, 6.99)	2, 3 or 4	1.23 (0.46, 3.27)	0	1.91 (0.68, 5.39)
					1	1.75 (0.59, 5.15)
TDCIPP	No	1.33 (0.57, 3.13)	1a or 1b	1.43 (0.55, 3.68)	X	0.82 (0.19, 3.5)
	Yes	2.74 (0.76, 9.87)	2, 3 or 4	1.81 (0.66, 4.95)	0	1.61 (0.58, 4.53)
					1	2.16 (0.72, 6.48)
TCEP	No	2.13 (0.89, 5.07)	1a or 1b	2.07 (0.79, 5.44)	X	9.70 (1.09, 86.2)*
	Yes	4.14 (1.01, 17.0)*	2, 3 or 4	3.18 (1.08, 9.38)*	0	1.23 (0.45, 3.37)
					1	4.06 (1.18, 13.9)*
TCIPP	No	0.95 (0.41, 2.21)	1a or 1b	1.19 (0.47, 3.02)	X	0.82 (0.2, 3.42)
	Yes	1.10 (0.33, 3.65)	2, 3 or 4	0.78 (0.29, 2.10)	0	1.05 (0.38, 2.87)
					1	0.95 (0.33, 2.70)
BDE-47	No	0.69 (0.30, 1.60)	1a or 1b	0.85 (0.34, 2.15)	X	0.61 (0.15, 2.55)
	Yes	0.96 (0.29, 3.13)	2, 3 or 4	0.65 (0.24, 1.72)	0	0.83 (0.30, 2.24)
					1	0.76 (0.27, 2.16)
BDE-99	No	0.85 (0.37, 1.93)	1a or 1b	0.75 (0.30, 1.89)	X	0.63 (0.15, 2.62)
	Yes	0.52 (0.16, 1.77)	2, 3 or 4	0.74 (0.28, 1.92)	0	0.86 (0.32, 2.32)
					1	0.67 (0.24, 1.89)
BDE-100	No	0.86 (0.37, 1.98)	1a or 1b	1.14 (0.45, 2.89)	X	0.63 (0.15, 2.66)
	Yes	0.98 (0.30, 3.23)	2, 3 or 4	0.67 (0.25, 1.79)	0	1.48 (0.53, 4.09)
					1	0.62 (0.22, 1.79)
BDE-153	No	0.98 (0.43, 2.24)	1a or 1b	0.80 (0.32, 2.00)	X	0.92 (0.23, 3.71)
	Yes	0.35 (0.10, 1.27)	2, 3 or 4	0.73 (0.28, 1.92)	0	1.37 (0.51, 3.72)
					1	0.38 (0.13, 1.15)
BDE-154	No	0.47 (0.14, 1.60)	1a or 1b	0.84 (0.33, 2.11)	X	1.23 (0.29, 5.18)
	Yes	0.93 (0.41, 2.14)	2, 3 or 4	0.72 (0.27, 1.89)	0	1.36 (0.5, 3.71)
					1	0.34 (0.11, 1.04)
BDE-209	No	2.70 (1.10, 6.61)*	1a or 1b	3.22 (1.16, 8.94)*	X	4.67 (0.83, 26.4)
	Yes	2.44 (0.69, 8.68)	2, 3 or 4	2.10 (0.76, 5.85)	0	3.22 (1.06, 9.79)*
					1	1.88 (0.64, 5.54)

536 *p<0.05

Table 4: Adjusted odds ratios by BRAF mutation status for FR exposure above the median (n=116).

Mixture	Individual FR	BRAF V600E Status	OR (95% CI)
Alternate BFRs	TBB	BRAF (+)	0.73 (0.28, 1.93)
		BRAF (-)	0.92 (0.27, 3.18)
		BRAF not assessed	0.37 (0.12, 1.18)
	TBPH	BRAF (+)	1.70 (0.62, 4.69)
		BRAF (-)	1.51 (0.41, 5.57)
		BRAF not assessed	0.75 (0.25, 2.25)
PFRs	TPHP	BRAF (+)	1.61 (0.59, 4.40)
		BRAF (-)	5.63 (1.18, 26.8)*
		BRAF not assessed	1.86 (0.60, 5.78)
	TDCIPP	BRAF (+)	1.09 (0.41, 2.92)
		BRAF (-)	2.01 (0.55, 7.41)
		BRAF not assessed	1.93 (0.63, 5.86)
	TCEP	BRAF (+)	2.03 (0.73, 5.65)
		BRAF (-)	3.76 (0.89, 15.9)
		BRAF not assessed	2.35 (0.76, 7.31)
	TCPP	BRAF (+)	1.03 (0.38, 2.80)
		BRAF (-)	1.01 (0.29, 3.55)
		BRAF not assessed	0.74 (0.25, 2.19)
Penta-BDE	BDE-47	BRAF (+)	0.88 (0.33, 2.34)
		BRAF (-)	1.16 (0.33, 4.00)
		BRAF not assessed	0.56 (0.19, 1.68)
	BDE-99	BRAF (+)	0.70 (0.26, 1.86)
		BRAF (-)	1.75 (0.49, 6.25)
		BRAF not assessed	0.46 (0.15, 1.40)
	BDE-100	BRAF (+)	1.10 (0.41, 2.95)
		BRAF (-)	1.75 (0.49, 6.29)
		BRAF not assessed	0.43 (0.14, 1.33)
	BDE-153	BRAF (+)	0.97 (0.37, 2.54)
		BRAF (-)	1.70 (0.48, 6.06)
		BRAF not assessed	0.33 (0.10, 1.07)
	BDE-154	BRAF (+)	1.09 (0.41, 2.90)
		BRAF (-)	1.25 (0.36, 4.42)
		BRAF not assessed	0.40 (0.13, 1.24)
Deca-BDE	BDE-209	BRAF (+)	1.84 (0.66, 5.15)
		BRAF (-)	14.2 (1.63, 123)*
		BRAF not assessed	1.42 (0.47, 4.28)

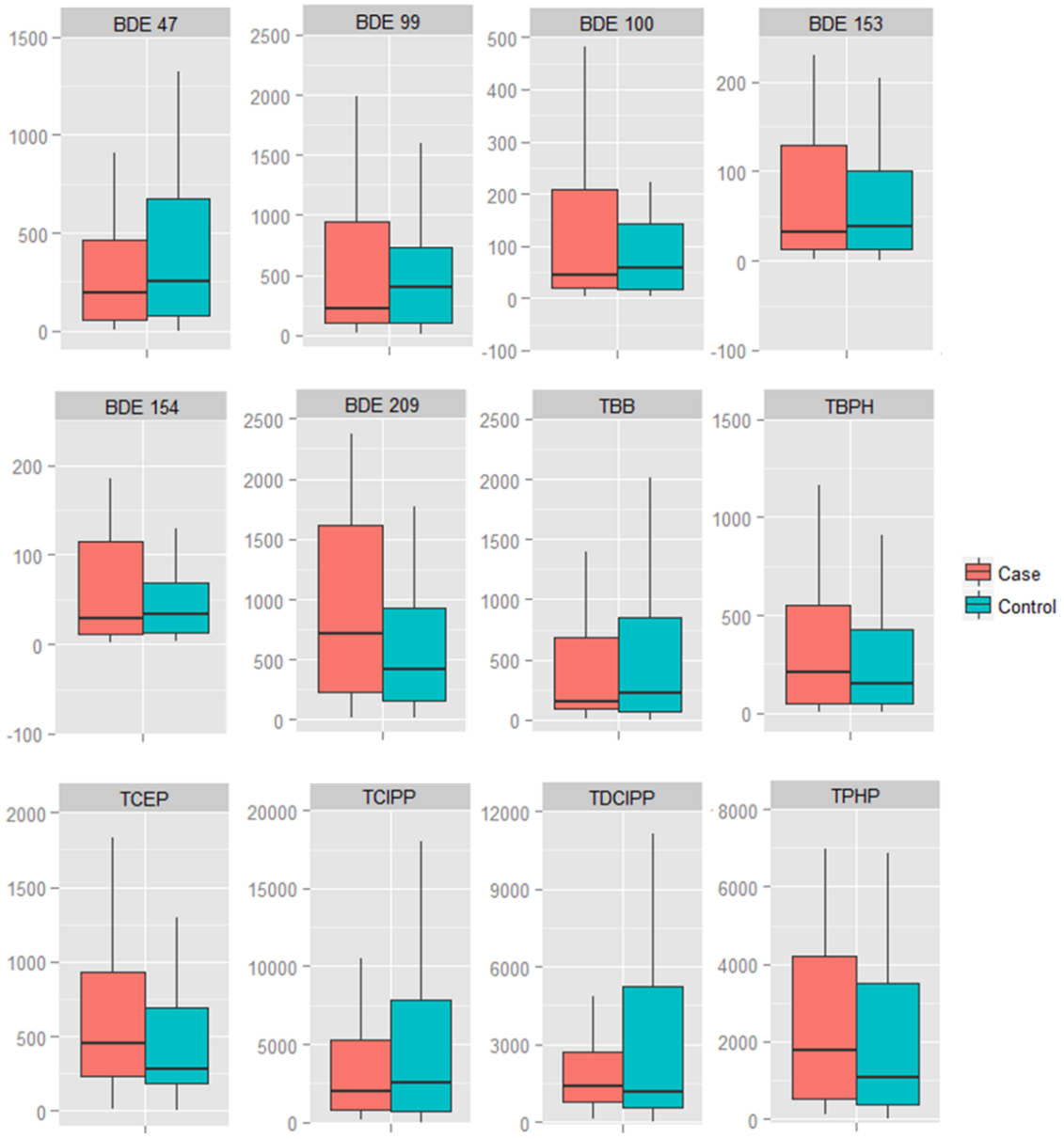
*$p<0.05$

Figure Legend

Figure 1:

Box plots of FR concentrations (ng/g dust) by case status (n=116). Outliers are not shown in plots.

Figure 1: Box plots of FR concentrations (ng/g dust) by case status (n=116). Outliers are not shown in plots.



Supplemental Material

EXPOSURE TO FLAME RETARDANT CHEMICALS AND THE OCCURRENCE AND SEVERITY OF PAPILLARY THYROID CANCER: A CASE-CONTROL STUDY

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Supplemental Table 1: Spearman Correlations between FRS in household dust (n=116)

	BDE 99	BDE 100	BDE 153	BDE 154	BDE 209	TBB	TBPH	TCIPP	TDCIPP	TCEP	TPHP
BDE 47	0.83 ***	0.87 ***	0.72 ***	0.70 ***	0.15	0.13	0.24 **	0.21 **	0.34 ***	0.16	0.35 ***
BDE 99		0.82 ***	0.70 ***	0.71 ***	0.17	0.36 ***	0.42 ***	0.27 **	0.34 ***	0.20*	0.41 ***
BDE 100			0.88 ***	0.88 ***	0.23 *	0.13	0.26 **	0.20 *	0.29 **	0.17	0.36 ***
BDE 153				0.88 ***	0.26 **	0.15	0.24 **	0.18	0.28 **	0.14	0.35 ***
BDE 154					0.31***	0.17	0.28 **	0.17	0.26 **	0.19 *	0.32 ***
BDE 209						0.24 **	0.28 **	0.13	0.27 **	0.20*	0.30 **
TBB							0.77 ***	0.20 *	0.28 **	0.15	0.35 ***
TBPH								0.28**	0.31 ***	0.21*	0.46 ***
TCIPP									0.33 ***	0.51 ***	0.26 **
TDCIPP										0.41 ***	0.33 ***
TCEP											0.33 ***

*** <.001

** <.01

* <0.05

Supplemental Table 2:
Adjusted odds ratios by AJCC Stage for FR exposure above the median (n=110).

Compound	AJCC Stage	OR (95% CI)
TBB	Stage 1	0.78 (0.33, 1.85) p=0.58
	Stage 2-4	0.38 (0.11, 1.29) p=0.12
TBPH	Stage 1	1.09 (0.45, 2.63) p=0.85
	Stage 2-4	1.53 (0.47, 4.94) p=0.48
TDCIPP	Stage 1	1.08 (0.44, 2.62) p=0.87
	Stage 2-4	4.13 (1.11, 15.3) p=0.03
TCEP	Stage 1	2.31 (0.93, 5.78) p=0.07
	Stage 2-4	3.05 (0.88, 10.6) p=0.08
TCPP	Stage 1	1.06 (0.44, 2.57) p=0.90
	Stage 2-4	0.88 (0.28, 2.69) p=0.82
TPP	Stage 1	2.02 (0.82, 5.01) p=0.13
	Stage 2-4	2.56 (0.75, 8.71) p=0.13
BDE-47	Stage 1	0.83 (0.35, 1.98) p=0.67
	Stage 2-4	0.64 (0.21, 1.98) p=0.44
BDE-99	Stage 1	0.38 (0.11, 1.24) p=0.11
	Stage 2-4	0.99 (0.42, 2.34) p=0.98
BDE-100	Stage 1	0.96 (0.40, 2.31) p=0.93
	Stage 2-4	0.82 (0.27, 2.52) p=0.73
BDE-153	Stage 1	0.98 (0.41, 2.31) p=0.95
	Stage 2-4	0.48 (0.15, 1.51) p=0.21
BDE-154	Stage 1	1.07 (0.44, 2.55) p=0.89
	Stage 2-4	0.41 (0.13, 1.33) p=0.14
BDE-209	Stage 1	2.29 (0.91, 5.74) p=0.08
	Stage 2-4	3.97 (1.06, 14.9) p=0.04

Supplemental Table 3: Adjusted odds ratios for PTC and by BRAFV600E mutation status for FR exposure above the median (n=116).

Serum BDE-47		Serum BDE-153	
Outcome	**OR (95% CI)**	**Outcome**	**OR (95% CI)**
PTC	0.75 (0.34, 1.63)	PTC	0.68 (0.31, 1.54)
BRAF (+)	0.58 (0.21, 1.60)	BRAF (+)	0.99 (0.38, 2.84)
BRAF (-)	1.06 (0.28, 4.04)	BRAF (-)	0.32 (0.08, 1.37)
BRAF not assessed	0.83 (0.29, 2.39)	BRAF not assessed	0.70 (0.23, 2.11)

Supplemental Figure 1: Study population consort.