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Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study

Kate Hoffman[a], Amelia Lorenzo[a], Craig M. Butt[a], Stephanie C. Hammel[a], Brittany Bohinc Henderson[b], Sanziana A. Roman[d], Randall P. Scheri[d], Heather M. Stapleton[a], Julie Ann Sosa[c,d,e,f,*]

[a] Nicholas School of the Environment, Duke University, Durham, NC 27708, United States
[b] Division of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, Wake Forest University Baptist Medical Center and Wake Forest Comprehensive Cancer Center, Winston-Salem, NC 27157, United States
[c] Department of Medicine, Duke University Medical Center, Durham, NC 27710, United States
[d] Department of Surgery, Duke University Medical Center, Durham, NC 27710, United States
[e] Duke Cancer Institute, Duke University Medical Center, Durham, NC 27710, United States
[f] Duke Clinical Research Institute, Duke University Medical Center, Durham, NC 27710, United States

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ABSTRACT

Background: Thyroid cancer is the fastest increasing cancer in the U.S., and papillary thyroid cancer (PTC) accounts for > 80% 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 worldwide 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

* Corresponding author at: Box DUMC 2945, Durham, NC 27710, United States.
E-mail address: julie.sosa@duke.edu (J.A. Sosa).

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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 migrate 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 United States 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; Brinton et al., 2007; Søgaard et al., 2016; Moeller and Fuhrer, 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 Fig. 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).

2.2. Clinical assessment

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

2.3. FRs in household dust

Upon enrollment, study personnel visited each participant's home to obtain environmental samples (e.g. household dust) and conduct study questionnaires. Participants were instructed not to vacuum their home for at least two days prior to their study visit. During the visit, the main living area of the home was vacuumed using a Eureka Mighty Might