

FLAME RETARDANT EXPOSURES AND THE INCIDENCE OF THYROID CANCER: IS THERE A LINK?

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Introduction

The incidence of thyroid cancer has dramatically increased world-wide over the last several decades¹. This observation has been almost exclusively the result of an epidemic of papillary thyroid cancer (PTC). While radiation exposure and obesity are established risk factors, little research has investigated the role of environmental exposures.

The flame retardants (FRs) polybrominated diphenyl ethers (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. Much less is known about the potential impact of other types of FRs; however, the organophosphate flame retardants (PFRs) have been associated with thyroid hormone disruption in several recent studies. Interestingly, clinical hyperthyroidism 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 severity². Additionally, several FRs are considered carcinogens and have been associated with the increased development of hepatocellular adenomas and carcinomas in chronically exposed rodents^{3,4}.

Because the impact of FR exposures on human thyroid cancer risk remains unknown, this study was undertaken to test the hypothesis that higher exposure to FRs in the home environment is associated with PTC occurrence and severity. This represents the first study to investigate relationships between PTC and many commonly used FRs detected in the home environment.

Materials and Methods

A case-control study design was used. From 2014-2016, patients diagnosed with PTC and referred to endocrinology at the Duke Cancer Institute were approached and invited to participate in this study. Control participants were recruited and matched to enrolled cases based on sex and age (within seven years of the cases' age at enrollment). To confirm that levels of exposure in the home were reflective of exposure occurring over the last several years (e.g. before diagnosis), inclusion was restricted to individuals that had lived in the same home for at least two years.

Upon enrollment, study personnel visited each participant's home to collect house dust and administer a questionnaire. The main living area of the home was vacuumed using methods used previously, and levels of 11 FRs in dust were assessed using previously published methods⁵. All study participants were asked to provide blood samples in which PBDEs were measured. Clinical

and pathologic information was obtained from each PTC case's medical records, including size of primary tumor, multifocality, status of cervical lymph nodes, and distant metastases, extra-thyroidal extension, and BRAF V600E mutation status.

FR concentrations were log-normally distributed, and preliminary analyses suggested that associations between FRs and outcomes were unlikely to be linear. As such, levels of each FR were dichotomized at the median value among controls to represent 'high' and 'low' exposure in predictive models. Logistic regression models were used to examine associations between exposure and case status while controlling for potential confounders. Standard polytomous regression (i.e. multinomial regression) analyses were used to evaluate relationships between exposure and outcomes with multiple levels (e.g. tumor size).

Results and Discussion

Reflecting known gender differences in PTC risk, our final study population was 78.6% female, and the mean age of participants was 48 years. Cases and controls were similar with respect to race and ethnicity, household income, and health history, and similar with respect to the number of years they reported living at the current address, which was more than 10 years for both.

FRs were detected in all house dust samples, and concentrations spanned several orders of magnitude. As a chemical class, PFRs were detected most frequently and in the highest concentrations. Compared to matched controls, PTC cases were significantly more likely to have high concentrations of TCEP and BDE-209 in their house dust. For example, those with dust BDE-209 levels above the median were 2.29 times ($p < 0.05$) as likely to be cases compared to those with house dust levels below the median.

FRs were also associated with markers of tumor aggressiveness. For example, high levels of BDE-209 were only associated with tumors contained in the thyroid, suggesting that BDE-209 may contribute to the risk of smaller, less aggressive PTCs. Conversely, higher levels of TCEP were associated with extrathyroidal extension, more advanced T-stage, and nodal metastasis. Associations between FRs and PTC also varied by the presence of the BRAF V600E mutation, with high exposure generally more strongly related to BRAF V600E(-) tumors. For example, participants with high levels of BDE-209 in house dust were 14.2 times ($p < 0.05$) as likely to be BRAF(-) cases compared to controls.

Of the 14 PBDEs measured in serum samples, only two were detected in more than 70% of serum samples. 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 ($p > 0.05$). There was no evidence of association between serum BDEs and PTC.

Our results from this case-control study suggest that exposure to some FRs in the home environment may be related to an 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 also 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. Given the increase in mortality associated with PTC, and the high financial demands placed upon thyroid patients for treatment and follow-up, more research is urgently needed to further investigate these associations, and determine if these trends are replicated in a larger cohort.

References

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