Application of two statistical approaches to assess breast cancer risk in association with exposure to mixtures of brominated flame retardants and perfluorinated alkylated substances in the E3N cohort.

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INTRODUCTION

Brominated flame retardants (BFR) and perfluorinated alkylated substances (PFAS) are two groups of substances suspected to act like endocrine disruptor chemicals (EDCs). Such substances are therefore thought to play a role in the occurrence of breast cancer. Previous studies that have attempted to elucidate the relationship between internal exposure levels of EDCs, such as PFAS and BFR, and breast cancer risk, have led to inconsistent results. There are several challenges to overcome when modelling the effects of exposure to such chemicals as mixtures, in particular the large correlation between these substances, the possibly non-linear effects they exert, and the possible interactions between them.

The present study aimed to investigate the relationship between circulating levels of 7 BFR (6 PDBE and 1 PBB) and 11 PFAS and the risk of breast cancer in a case control study nested in the E3N French prospective cohort by performing two methods: Principal Component Regression (PCR), a classic method used in epidemiology to deal with multicollinearity, and Bayesian Kernel Machine Regression (BKMR), a novel statistical method that addresses the above-mentioned challenges.

METHODOLOGY

194 post-menopausal breast cancer cases and 194 controls were included in the present study. Circulating levels of BFR and PFAS were measured by gas chromatography coupled to high-resolution mass spectrometry and liquid chromatography coupled to tandem mass spectrometry, respectively. The first statistical approach was based on a Principal Component Analysis (PCA), followed by logistic regression models including the identified principal components as main exposure variables. The second approach used BKMR models with hierarchical variable selection, this latter being suitable for highly correlated exposures. BKMR estimates the exposure-response surface accounting for interactions and non-linear relationships by flexibly modelling exposures. Both approaches were also ran separately for Oestrogen Receptor positive (ER+) and Oestrogen Receptor negative (ER-) breast cancer cases.

RESULTS

PCA identified four principal components accounting for 68 % of the total variance. Only Component 3 and the fourth quintile group of Component 4 showed a marginal association with overall and ER+ breast cancer risk. No statistically significant association between BFR and PFAS mixtures and breast cancer was identified using BKMR models, although the credible intervals obtained were very wide. A negative cumulative effect of BFR and PFAS on ER- breast cancer risk, and a positive cumulative effect on ER+ breast cancer risk were highlighted using BKMR models. However, neither of these associations were statistically significant.

DISCUSSION

Combining the results of these two approaches has allowed us to identify components associated with breast cancer risk, and then further hypothesise which substances contributing to these components could be responsible for the association identified, highlighting the sense of relation and taking multicollinearity into account. However, the insufficient number of subjects made it impossible to identify any potentially significant association using the BKMR approach, which resulted in very large credible intervals. Further studies evaluating mixtures of substances on larger sample sizes are needed.