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Breast cancer among women in Michigan following exposure to brominated flame retardants

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Abstract

In this updated follow-up, we investigated the breast cancer experience among women in Michigan exposed to brominated flame retardants, some 30 years following exposure. Michigan residents were enrolled in a study cohort after exposure to polybrominated biphenyls (PBBs) through the consumption of contaminated food products. PBB concentrations were measured in serum at the time of enrolment. Cancer experience was determined by linkage to the Michigan Cancer Registry. We conducted a nested case–control study that included 51 women diagnosed with breast cancer during 1974–2004 and 202 age-matched controls. While the data suggest an increase in breast cancer risk with higher PBB exposure, this did not reach statistical significance. The OR of having breast cancer among women with PBB concentrations ≥10 ng/mL compared to women with PBB concentrations at or below the limit of detection of 1 ng/mL was 2.60, 95% CI 0.93 to 7.27, (p=0.07), when adjusted for age and family history of cancer in a first-degree female relative. It

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remains important to examine exposure to brominated chemicals and possible health effects, and to continue following the cancer experience of participants in this study.

INTRODUCTION

The Michigan Long–Term PBB Study was initiated following an industrial accident in Michigan in the 1970s. AVelsicol Chemical Company manufactured two products, FireMaster, a brominated flame retardant mixture of polybrominated biphenyls (PBB), and NutriMaster, a feed supplement for livestock. During May 1973, the company inadvertently shipped FireMaster instead of NutriMaster to the Michigan Farm Bureau Services, where it was mixed into animal feed and shipped to feed mills across the state. Farms used the PBB–contaminated feed, which led to widespread contamination of meat, milk, eggs and other animal products. Michigan residents ate contaminated food for nearly a year before the problem was discovered and the affected farms were quarantined. While exposure to PBB was statewide, the Michigan general population had PBB levels that were lower than those of the affected farm families.[1] Additional details of the incident have been previously published.[2]

PBB was added to plastics, textiles and electrical devices, to reduce flammability. The USA discontinued the manufacture of PBB following this incident, but PBB remains a concern because of its persistence in humans and the environment and similarity, in structure and toxicity profile, to other brominated flame retardants still in use. The estimated half-life of PBB ranges from 13 to 29 years in females.[3]

Exposure to endocrine disruptors may increase the risk of hormone-dependent cancers, because they mimic or block natural hormones in the body, such as oestrogen. In animal studies, PBB has induced tumours in mice and rats.[4] PBB has recently been classified as ‘probably carcinogenic to humans’ by the International Agency for Research on Cancer [5] and ‘reasonably anticipated to be carcinogenic to humans’ by the National Toxicology Program.[6]

Two earlier studies report on the cancer experience in this cohort. Henderson *et al*[7] investigated 20 breast cancer cases (follow-up to 1992) and Hoque *et al*,[8] 25 breast cancer cases (follow-up to 1993). Although based on small numbers, both studies found non-significant increases in the risk of breast cancer in women with higher PBB exposure. In this updated follow-up, we examine the association between breast cancer and serum PBB levels, and include the cancer experience, some 30 years following exposure.

METHODS

Study population

In 1976, the Michigan Department of Community Health (MDCH) began recruiting Michigan residents if they lived on or received food from a farm quarantined by the Michigan Department of Agriculture (based on farm animals exceeding PBB levels of 0.3 parts per million (ppm) in milk or meat or 0.05 ppm in eggs[9]). Participants completed enrolment interviews, capturing demographic information, medical history and exposures,

and most provided a serum sample and have been actively followed with updates of vital records, health and exposure information.

PBB assessment

Michigan residents were exposed to a mixture of PBB of mostly PBB–153 or 2,2′4,4′5,5′–hexabromobiphenyl (~60%). Serum samples collected from participants at enrolment (1976–1978) were analysed by the MDCH Bureau of Laboratories, using gas chromatography and employing an electron capture detection quantification method.[10] The analytical methods of PBB detection had a coefficient of variations ranging from 7.1% to 14% and recovery ranges of 80–90%.[10] Serum PBB measurements were collected from non-fasting participants and were not adjusted for serum lipid levels.

Matching individuals to the cancer registry

Participants were matched to the Michigan Cancer Registry by the MDCH Division of Vital Records and Health Statistics, using a stepwise probabilistic matching programme that compared discrete combinations of demographic information to identify matches. Results were manually reviewed by Vital Records staff for final determination. De-identified matches were provided to investigators at the University of Illinois and Emory University, in encrypted files. The procedures were approved by the Institutional Review Boards at the University of Illinois, Emory University and the MDCH.

Case–control ascertainment

In the Michigan Long-Term PBB Study, there were 1930 females born before 1 July 1973, the date when the contaminated feed was suspected to be distributed to farms statewide. Of these, 1749 had an enrolment interview and serum PBB measurements taken, and were deemed eligible for the study. We identified 51 invasive breast cancer cases diagnosed from 1974 to 2004. ‘Invasive’ was determined from the cell behaviour codes identifying the primary cancer of the breast (C50.0–C50.9) with malignant behaviour (behaviour code of 3). Prior to establishment of the Michigan Cancer Registry (before 1985), cases were identified from study diagnostic follow-ups, and were physician confirmed (n=13). All other cases were identified from the Michigan Cancer Registry (n=38). Dates of death were confirmed from the National Death Index mortality data files. Women who had a previous breast cancer diagnosis, any other cancer diagnoses from another site or an unknown site (except non-melanoma skin cancer or carcinoma in situ, not including in situ bladder) or who died from cancer (underlying cause or related cause), were not eligible to act as controls (n=128 excluded).

Statistical analysis

We matched four controls per case, using an incidence density sampling method.[11] Cases and controls were age matched in 5-year strata based on age during the exposure incident, and controls had to remain in the study and survive to at least the same time as the matched case’s diagnosis date. Fifty cases were matched to four controls, with the remaining one case matched to two controls. We considered well-established risk factors for breast cancer (age,

family history and age at first live birth).[12] We also considered history of alcohol consumption, smoking history and body mass index at enrolment.

As a result of a skewed distribution, we categorised PBB: at or below the limit of detection (≤1 ng/mL) and split at the upper quartile (10 ng/mL), to capture the highly exposed women. PBB was also modelled as a log-transformed continuous variable. We evaluated ORs for incident breast cancer, using conditional logistic regression. We examined age-adjusted associations between risk factors by case–control status and investigated whether factors were confounders by adding them one at a time to a model that contained only PBB exposure. As a result of the small sample sizes, we assessed confounding by a change in OR (>10% change in the effect estimate). Statistical analyses were conducted using SAS (V.9.3; SAS Institute, Cary, North Carolina, USA).

RESULTS

Women were exposed to PBB when they were on average 42 years during the PBB incident (age at 1 July 1973) and <10% were younger than 18 years at the time. The geometric mean enrolment PBB levels were 2.9 ng/mL for cases and 2.2 ng/mL for controls. Older women had slightly higher enrolment PBB levels. The mean age at breast cancer diagnosis was 61 years and the average time from exposure to breast cancer diagnosis was 18 years. Although not statistically significant, cases reported more frequently to having a family history of cancer in a first-degree female relative, compared to controls. When PBB was log-transformed and modelled continuously, the OR was not significant (OR=1.198, 95% CI 0.945 to 1.520). When PBB was modelled categorically, the OR for breast cancer incidence was elevated for those with PBB ≥10 ng/mL compared to PBB ≤1 ng/mL (OR=2.60, 95% CI 0.93 to 7.27), but did not reach statistical significance (p=0.07) when adjusted for age and family history of cancer in a first-degree female relative (table 1).

DISCUSSION

In this updated report of breast cancer experience spanning 30 years, the data suggest an increase in breast cancer risk with higher PBB exposure, but this was not statistically significant. These findings are consistent with two earlier reports on breast cancer in this cohort.[78] In addition to a long follow-up of women, our study has a biological measure of exposure ascertained many years prior to breast cancer diagnosis, and a control group that was drawn from the same population as the cases.

The main risk factors for breast cancer indicate that risk increases with older age, having a first-degree female relative with breast cancer and older age at first live birth.[12] Several risk factors were available on a subset of our study sample (22 cases and 77 controls), for self-reported age at menarche, history of hormone replacement and months of lactation (from a 1997 to 1998 questionnaire), but we did not find these associated with breast cancer (results not shown). We did not have information on oestrogen receptor status. We were also unable to ascertain breast cancer cases among women who moved out of the state of Michigan before they were diagnosed. However, we would only expect this loss to bias our results if

the women who moved differed from those who stayed, in PBB level and breast cancer incidence.

Our study included women who were accidentally exposed to high levels of PBB. While we did not find statistically significant associations of breast cancer incidence with higher serum PBB concentrations, this may be due to limited power and not lack of association, given our small sample sizes. We observed nine breast cancer cases in the high PBB exposure group, where we would have expected five cases (observed: 17.7% cases in referent group, PBB ≤1 ng/mL; expected: 17.7% of 27 women in the PBB ≥10 ng/mL group=4.8). It remains important to follow this cohort for adverse health outcomes, and it is important for women who were exposed to get regular breast cancer screening.

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What this paper adds

- This study expands on the breast cancer experience of residents exposed to varying levels of a class of brominated flame retardants, polybrominated biphenyls (PBBs).
- The evidence to date from International Agency for Research on Cancer suggests that PBBs are ‘probably carcinogenic to humans. Thus, ’ continued research of the cancer experience in this cohort is recommended.
- The findings in this study may provide information about the carcinogenic effects of similar chemicals with potential endocrine disrupting properties.

Table 1

Descriptive characteristics and ORs for incident breast cancer among women in the Michigan Long-Term PBB Study

Characteristics	Cases (n=51)		Controls (n=202)			
Continuous variables	**Minmum–Maximum**	**Mean (SD)**	**Minimum–Maximum**	**Mean (SD)**		
Age at exposure (years)	10.2–72.4	42.7 (14.4)	9.4–74.8	42.3 (14.0)		
Age at diagnosis (years)	28.9–90.3	61.2 (13.9)	–	–		
Years from exposure (July 1973) to diagnosis	1.0–30.1	18.5 (8.1)	–	–		
Body mass index at enrolment (kg/m^2)	19.6–40.7	25.4 (4.5)	15.0–43.3	25.9 (5.1)		
PBB concentration at enrolment (ng/mL) *	ND-570.0	2.9 (2.4)	ND-194.0	2.2 (1.8)		
Categorical variables	**N**	**Per cent**	**N**	**Per cent**	**Adjusted † OR (95% CI)**	**Adjusted p Value**
Enrolment PBB (75th P=10 ng/mL) ‡						
≤1 (at or below LOD)	17	33.3	79	39.1	1.00	–
>1–9	25	49.0	105	52.0	1.17 (0.59 to 2.33)	0.65
≥10	9	17.7	18	8.9	2.60 (0.93 to 7.27)	0.07
Family history of cancer in a first-degree female relative						
No	28	54.9	137	67.8	1.00	–
Yes	14	27.5	36	17.8	1.90 (0.92 to 3.93)	0.08
Not asked	9	17.6	29	14.4	–	–
Age at first live birth (years)						
<21	10	32.3	57	41.3	1.00	–
21–25	13	41.9	50	36.2	1.47 (0.59 to 3.67)	0.41
≥26	8	25.8	31	22.5	2.15 (0.62 to 7.47)	0.23
History of alcohol consumption, at enrolment						
Total abstainer	26	54.2	101	52.1	1.00	–
Former/present user	22	45.8	93	47.9	0.88 (0.46 to 1.68)	0.71
History of smoking cigarettes, at enrolment						
Non-smoker	38	77.6	150	76.1	1.00	–
Former/present smoker	11	22.4	47	23.9	0.94 (0.44 to 2.02)	0.88
Drank milk or ate meat or eggs from quarantined farm during 1973–1974						
No	4	7.8	29	14.4	1.00	–

Characteristics	Cases (n=51)		Controls (n=202)			
Continuous variables	**Minmum–Maximum**	**Mean (SD)**	**Minimum–Maximum**	**Mean (SD)**		
Yes	47	92.2	173	85.6	1.94 (0.65 to 5.78)	0.23
Ever lived on a quarantined farm						
No	20	39.2	92	45.5	1.00	–
Yes	31	60.8	110	54.5	1.27 (0.68 to 2.37)	0.45

*ND=not detectable; geometric mean and SD of the geometric mean are shown.

†Controls matched 1:4 ratio by 5-year age stratum, all models are age adjusted.

‡Exposure model adjusted for age and family history of cancer in first-degree female relative.

LOD, limit of detection; ND, not detectable; PBB, polybrominated biphenyls.