

Serum levels of beta-hexachlorocyclohexane, hexachlorobenzene and polychlorinated biphenyls and breast cancer in Mexican women

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Information on the association between exposure to beta-hexachlorocyclohexane (β -HCH), hexachlorobenzene (HCB) or polychlorinated biphenyls (PCBs) and the incidence of breast cancer is inconclusive. However, exposure to such compounds is a public health concern in Mexico and is subject to recent regulation. Serum levels of β -HCH, HCB and PCBs were analysed in 95 histologically confirmed breast cancer cases and 95 hospital controls, 20–79 years of age, from Mexico City, enrolled between March 1994 and April 1996. After adjusting for established risk factors, there was no evidence of a relationship between β -HCH, HCB and PCBs and breast cancer risk (OR for β -HCH tertile 3 versus tertile 1: 1.05 95% CI 0.46–2.40; OR for HCB tertile 3 versus tertile 1: 0.46 95% CI 0.20–1.07; OR for PCBs 1.31 95% CI 0.33–5.21 for the high category of exposure). This study lends no support to the case for a role for β -HCH, HCB or PCBs in breast cancer aetiology.

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Key words: Beta-hexachlorocyclohexane, breast cancer, case-control, hexachlorobenzene, Mexico, organochlorine compounds, polychlorinated biphenyls, serum levels.

Introduction

Beta-hexachlorocyclohexane (β -HCH), hexachlorobenzene (HCB) and the group of chemical compounds known as polychlorinated biphenyls (PCBs) are persistent lipophilic organochlorine substances that mimic hormonal activity (Li and Li, 1998). This raised concern that they might contribute to the development of breast cancer.

In 1990, a study in Finland (Mussalo-Rauhamaa *et al.*, 1990) showed significantly higher levels of β -HCH in breast adipose tissue samples from breast cancer patients than from individuals who died from accidents. In contrast, other case-control (Dewailly *et al.*, 1994; Güttes *et al.*, 1998; Zheng *et al.*, 1999a,b; Aronson *et al.*, 2000) and prospective (Hoyer *et al.*, 1998, 2000; Dorgan *et al.*, 1999) studies found no association between β -HCH and breast cancer risk. A more recent case-control study (Demers *et al.*, 2000) reported that β -HCH increases the risk of exhibiting more aggressive breast malig-

nant tumours (i.e. tumours ≥ 2 cm and lymph node invasion).

Inconsistent results also come from studies of HCB exposure and breast cancer risk. Case-control studies (Mussalo-Rauhamaa *et al.*, 1990; Falck *et al.*, 1992; Dewailly *et al.*, 1994; Güttes *et al.*, 1998; Moysich *et al.*, 1998; Zheng *et al.*, 1999a,b; Aronson *et al.*, 2000) and a recent prospective study (Hoyer *et al.*, 2000) have shown no association between HCB and breast cancer risk, however, a previous prospective study (Dorgan *et al.*, 1999) found a 2.6-fold increase in breast cancer risk among women whose blood was collected close to the time of diagnosis and a risk of 7.1 was found among postmenopausal women with positive oestrogen receptor tumours in a case-control study (Liljegren *et al.*, 1998).

Significant increases of breast cancer risk due to the exposure to some PCBs have been reported from one prospective (Dorgan *et al.*, 1999) and some case-control studies (Wassermann *et al.*, 1976; Falck *et al.*, 1992; Dewailly *et al.*, 1994; Güttes *et al.*, 1998;

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Moysich *et al.*, 1999; Aronson *et al.*, 2000; Demers *et al.*, 2000), whereas other studies are negative (Unger *et al.*, 1984; Mussalo-Rauhamaa *et al.*, 1990; Wolff *et al.*, 1993, 2000a,b; Krieger *et al.*, 1994; Hunter *et al.*, 1997; Aschengrau *et al.*, 1998; Hoyer *et al.*, 1998, 2000; Liljegren *et al.*, 1998; Moysich *et al.*, 1998; Helzlsouer *et al.*, 1999; Aronson *et al.*, 2000).

In Mexico, although regulations for the production and importation of HCH and HCB were issued in the early 1990s (CICOPLAFEST, 1994; SECOFI, 1996), old imported equipment containing PCBs is still being used (Instituto Nacional de Ecología, 1996). Due to the long persistency of these compounds in the environment, human exposure is a public health concern in the country.

In this paper we present the results from a hospital-based case-control study among Mexican women, focusing on the potential relationship between serum levels of β -HCH, HCB and PCBs (measured as a mixture of Aroclor 1260) and the risk of breast cancer.

Materials and methods

As an arm of a larger hospital-based case-control study performed in three large tertiary level public hospitals of Mexico City, between March 1994 and April 1996 (López-Carrillo *et al.*, 1997) we recruited 95 histologically confirmed new breast cancer patients and 95 age-matched (± 3 years) non-cancer controls.

Cases matched to controls on age (± 3 years) and residence in Mexico City were women between 20 and 79 years of age with a histologically confirmed breast carcinoma (10.5% had *in situ* breast cancer tumours), and no previous treatment for breast cancer.

Controls were identified at the clinical wards of the participating hospitals, with the exception of gynaecology and oncology. The most frequent diagnoses among the controls were: injuries (17.89%), problems of the genitourinary system (10.85%), diseases of the blood and the circulatory system (9.48%), digestive tract disorders (9.47%), ill-defined conditions (5.26%), osteomuscular and connective tissue disorders (4.21%), diseases of the respiratory system (4.21%) and, the nervous system (3.16%). Other smaller categories included were infectious diseases and nutritional disorders.

Data on reproductive histories, socio-economic characteristics, occupation and diet were gathered by direct interviews, immediately after obtaining an

informed consent. Height and weight were measured to estimate the body mass index (Quetelet Index, kg/m²). Interviews were completed for 81% of the eligible cases and 72% of the controls.

Ten millilitres of venous blood were drawn from each woman before starting cancer treatment using sterile Vacutainers. The serum was separated by centrifugation and frozen at -20°C in glass vials (pre-washed with hexane) and covered with a Teflon cap.

Chemical analyses

β -HCH and HCB levels were determined for all 190 serum samples. Aliquots of 1–2 ml were analysed by electron capture gas-liquid chromatography (EC-GLC) according to the protocol recommended by the US Environmental Protection Agency (United States Environmental Protection Agency, 1981, 1993). Each human serum sample was spiked with aldrin, which had an average recovery rate of $96.4 \pm 10.8\%$. In addition, 30 bovine serum spiked quality control samples with β -HCH and other selected organochlorines (i.e. β -HCH, aldrin, etc.) showed a $95.5 \pm 8.6\%$ of recovery for β -HCH. Serum lipids were measured according to the gravimetric method (Folch *et al.*, 1957). Concentrations were reported on the basis of ppb lipid weight (ng/g). The detection limit of the method was 53.0 ng/g for β -HCH and 27.0 ng/g for HCB.

For PCBs, serum samples were purified in silica gel (Burse *et al.*, 1990) derivatized by perchlorination with antimony pentachloride to yield decachlorobiphenyl (Huckins *et al.*, 1974) and determined by EC-GLC. The amount of decachlorobiphenyl present in samples was expressed as Aroclor 1260 mixture and expressed on a lipid basis (ng/g) (United States Environmental Protection Agency, 1980). From each analytical run, two samples were randomly selected for internal quality control purposes. One was a duplicate of the selected sample and the other was spiked with 120 ppb of Aroclor 1260. The coefficient of variation for the samples analysed in duplicate was $11.5\% \pm 10.8$. The mean efficiency for the reaction of Aroclor 1260 to DCB was $91.5\% \pm 4.09$. The limit of detection for the PCBs method was 26 ng/g in lipid bases.

Statistical analyses

The age-adjusted effects of selected reproductive factors on breast cancer risk were estimated by fitting conditional logistic regression models to the data.

The serum levels of β -HCH, HCB and PCBs from cases and controls were compared using the

Wilcoxon rank sum test. The 5 and 95 percentiles were calculated as a measure of data dispersion.

For calculations of odds ratios (OR) and 95% confidence interval (95% CI), serum levels of β -HCH, HCB were categorized in tertiles, on the basis of the distribution observed among the controls. The PCBs distribution was skewed and could not be normalized, thus, PCBs serum levels were categorized as <26.1 (which was the detection limit) 26.1–833 (i.e. from the detection limit to ‘traces’) and >833. The risk for developing breast cancer was estimated by fitting conditional logistic regression models according to the already mentioned categories. Potential confounders included in the final models were: age at menarche, number of children and age at first birth (≥ 3 children and <20 years at first birth, <3 children and <20 years at first birth, ≥ 3 children and ≥ 20 years at first birth, <3 children and ≥ 20 years at first birth and nulliparous), lifetime lactation (months), menopausal status, body mass index (kg/cm²) and familial history of breast cancer.

The exposure categories of β -HCH, HCB and PCBs were entered into the multivariate models as continuous data to test for trend. All analyses were

performed using the statistical software STATA 5.0 (Stata Corporation, College Station, Texas, USA).

Results

The effect of known determinants of breast cancer in the study population is shown in Table 1. No effect on breast cancer risk was observed in relation to age at menarche or menopausal status. Non-significant but increased odds ratios were detected for the comparison between the highest and lowest category of: number of children, age at first pregnancy, Quetelet Index and history of familial breast cancer. In contrast, total history of breastfeeding seemed to confer protection for breast cancer, although this relationship did not reach statistical significance.

Levels of β -HCH, HCB and PCBs did not differ significantly between cases and controls in the study population (Table 2). PCBs had the highest percentage of positive samples (87.89%), followed by β -HCH (78.42%). Less than a half of the serum samples contained detectable levels of HCB (42.63%).

Table 1. Characteristics of the study population

Variable	OR	95% CI
Age at menarche (years)		
≥ 12	1.0	–
<12	0.85	0.38–1.89
Parity		
≥ 4	1.0	–
1–3	2.36	1.19–4.66
Nulliparous	2.11	0.86–4.67
Age at first pregnancy		
<20	1.0	–
20–24	2.24	0.90–5.62
≥ 25	4.11	1.32–12.80
Duration of lactation first live birth (months)		
0	1.0	–
1–6	0.49	0.17–1.36
7–12	0.38	0.13–1.11
>12	0.31	0.08–1.22
Duration of lactation all births (months)		
0	1.0	–
1–6	0.45	0.10–2.09
7–12	0.44	0.09–2.23
>12	0.26	0.07–0.97
Menopausal status (%)		
Premenopausal	1.0	–
Postmenopausal	1.11	0.45–2.73
Family history of breast cancer (%)		
No	1.0	–
Yes	2.60	0.93–7.29
Quetelet Index (kg/m ²)		
<20–24	1.0	–
25–29	0.61	0.31–1.22
≥ 30	1.65	0.73–3.72

Table 2. β -HCH-, HCB and PCBs serum levels (ppb) in the study population

Compound	Cases	Controls	P-value ^a	Positive samples (%)
β -HCH (ng/g)				
Median	104.16	92.98		
(5%, 95%)	53.29–418.54	53.29–270.77	0.41	78.42
(n)	(95)	(95)		
HCB (ng/g)				
Median	27.69	27.69		
(5%, 95%)	27.69–69.44	27.69–87.72	0.24	42.63
(n)	(95)	(95)		
PCBs (ng/g)				
Median	833	833		
(5%, 95%)	26–20010.17	26–6078.1	0.27	87.89
(n)	(95)	(95)		

^aWilcoxon rank-sum test.

Table 3. Adjusted odds ratios for the effect of β -HCH-, HCB and PCBs on breast cancer risk

Compound	Cases	Controls	OR ^a	95% CI	OR ^b	95% CI	P-value ^c
β -HCH (ng/g)							
53.29–63.0	27	31	1.0	–	1.0	–	
63.0–114.58	29	33	1.03	0.51–2.09	0.65	0.28–1.51	
114.58–612.98	39	31	1.45	0.71–2.94	1.05	0.46–2.40	0.80
(number of pairs)	(95)						
HCB (ng/g)							
≤27.69	59	50	1.0	–	1.0	–	
27.70–39.06	18	23	0.65	0.30–1.39	0.58	0.24–1.39	
39.06–191.66	18	22	0.72	0.36–1.45	0.46	0.20–1.07	0.053
(number of pairs)	(95)						
PCBs (ng/g)							
≤26.0	13	10	1.0	–	1.0	–	
26.01–833	59	71	0.75	0.32–1.78	0.63	0.23–1.76	
>833	23	14	1.42	0.45–4.52	1.31	0.33–5.21	0.57
(number of pairs)	(95)						

^aAdjusted by age.

^bAdjusted by age at menarche (years), number of children and age at first birth (≥3 children and <20 years at first birth, <3 children and <20 years at first birth, ≥3 children and ≥20 years at first birth, <3 children and ≥20 years at first birth, nulliparous), lifetime lactation (months of breastfeeding), family history of breast cancer (yes/no), menopausal status (pre/post), Quetelet Index (kg/m²).

^ct-test for trend.

Adjusted odds ratios for breast cancer by serum levels of β -HCH, HCB and PCBs on a lipid basis are shown in Table 3. Compared with tertile 1, the adjusted odds ratios from β -HCH for tertiles 2 and 3 were OR 0.65 (95% CI 0.28, 1.51) and OR 1.05 (95% CI 0.46, 2.40) for HCB levels (OR 0.58; 95% CI 0.24, 1.39 and OR 0.46; 95% CI 0.20, 1.07). Neither the contrast of the highest category of PCBs exposure versus the lowest uncovered evidence for any effect on breast cancer risk (OR 1.31; 95% CI 0.33, 5.21).

Discussion

The results of this study provide no evidence of a relationship between the exposure of β -HCH and HCB, PCBs (measured as Aroclor 1260) and breast cancer risk.

HCH or BHC used to be generic terms for referring to a mixture of five isomers, which may be the oldest organochlorine substances used as insecticides (Kutz *et al.*, 1991). Because the α - and γ -isomers are biotransformed more rapidly, levels of HCH determined in human tissue samples will predominantly contain the β -isomer (Klaassen *et al.*, 1986). Since 1978, four of these isomers have been banned in the USA and only the γ -isomer (lindane or β -HCH or γ -BHC) is still in use (Kutz *et al.*, 1991). In Mexico, the order prohibiting the sale and use of the HCH isomers mixture was issued in 1991 (CICOPAFEST, 1994; SECOFI, 1996).

Our findings regarding β -HCH are consistent with the most recent studies (Zheng *et al.*, 1999a,b; Aronson *et al.*, 2000; Hoyer *et al.*, 1998, 2000; Dorgan *et al.*, 1999). Mussalo-Rauhamaa *et al.* (1990) found higher levels of β -HCH in 24 biopsies

of adipose breast tissue from breast cancer cases, than in 16 post-mortem adipose breast tissue specimens obtained from women dying accidentally. There are important differences between our study and the one performed by Mussalo-Rauhamaa *et al.* (1990), in which biopsies of breast tissue from living patients were compared with post-mortem breast tissue samples. Hence, a major concern is whether post-mortem specimens represent the actual serum levels of β -HCH expected to exist in the general population. If not, they could bias the odds ratio in any direction.

It is still possible that β -HCH increases the risk of higher breast cancer tumours with lymph node involvement, as reported recently by Demers *et al.* (2000). Further studies including sufficient number of breast cancer cases with lymph node involvement are necessary to exclude a role of β -HCH in regard to more aggressive breast cancer tumours.

HCB used to be used as an agricultural fungicide. Its production was stopped in the USA (Kutz *et al.*, 1991) in the 1970s. In Mexico, HCB is not produced and its importation was prohibited 10 years ago (CICOPLAFEST, 1994; SECOFI, 1996).

The lack of association between HCB serum levels and breast cancer risk observed in our study is consistent with the results of several previous studies (Mussalo-Rauhamaa *et al.*, 1990; Falck *et al.*, 1992; Dewailly *et al.*, 1994; Güttes *et al.*, 1998; Moysich *et al.*, 1998; Zheng *et al.*, 1999a,b; Aronson *et al.*, 2000; Hoyer *et al.*, 2000). However, Dorgan *et al.* (1999) found a positive significant association between HCB and breast cancer among women whose blood was collected around 2.7 years or less from the date of their diagnoses, but not among those sampled more than 2.7 years after diagnosis. These findings suggest a potential for HCB to act as a promoter and are not consistent with recent case-control studies in which biological samples were taken around the date of the diagnosis (Zheng *et al.*, 1999a,b; Aronson *et al.*, 2000). Due to the lack of evaluation of potential interactions between HCB levels, the time of sample collection and breast cancer risk in prospective studies (Hoyer *et al.*, 2000), a relationship between HCB and the presence of breast cancer metastasis cannot be ruled out.

PCB is a generic term for 209 different chemical compounds. Of those, about 130 may still be present in commercial products (World Health Organization, 1993). PCBs were extensively used as electrical insulators, coolants and lubricants in transformers and capacitors. Other uses included surface coatings and the production of plastics, adhesives, inks and pesticides. The manufacture of PCBs ceased in the

US in 1977 (Kutz *et al.*, 1991), but in Mexico the import of equipment containing PCBs was allowed until the early 1980s. Currently in Mexico, an estimated 8000 tons of PCBs are still in the electrical power sector, mainly in operational equipment and as residues (Instituto Nacional de Ecología, 1996).

In our study, PCB levels were much higher than those observed by Wolff *et al.* (1993) and Krieger *et al.* (1994), using serum samples of American women taken between 9 and 37 years ago. Almost 20% of our study population had PCB levels above 833 ppb, corresponding to the highest levels found in the above mentioned studies (29.4 ng/ml in wet basis). Therefore, current blood levels of PCBs in Mexico are a reflection of the exposure to prevalent sources of these compounds in the country.

The negative association reported in this study between PCBs and breast cancer risk should be interpreted with caution. First, the method that we used to measure PCBs is less sensitive than other current methods, thus a higher magnitude of non-differential measurement error could bias the odds ratio towards the null value. Second, no information on the type and level of specific congeners was available to further evaluate subgroups defined on the basis of their oestrogenic potential.

Moderately chlorinated PCB congeners no. 99 (Dewailly *et al.*, 1994), no. 105 (Aronson *et al.*, 2000), no. 118 (Güttes *et al.*, 1998) and no. 138 (Dorgan *et al.*, 1999) have been associated with an increased risk of breast cancer. Congeners no. 105 and no. 118 have been characterized as anti-oestrogenic dioxin-like compounds. This is incompatible with the oestrogenic origin of breast cancer, thus the observed association between those two congeners and breast cancer is likely to be a chance-occurrence.

Congener no. 138 is persistent and has a limited dioxin activity (Wolff *et al.*, 1997). It has been associated with an increased breast cancer risk when blood is collected near the time of diagnosis, but is inversely associated when the interval is longer. While no clear explanation is available for this interaction the potential role of congener no. 138 in breast cancer aetiology requires further attention.

Marginal significant higher levels of congener no. 99 were found in nine women with ER-positive breast cancer compared with 17 controls (Dewailly *et al.*, 1994). Although it is biologically plausible that this congener could play a role in breast cancer aetiology (induces phenobarbital as well as CYP1A and CYP2), causation cannot be established from only one positive study.

In a recent study, 56 congeners were significantly associated with an increase in breast cancer risk among those women with genetic polymorphism in the cytochrome P4501A1 (CYP1A1) (Moysich et al., 1999), but being the first report on the topic, such findings need to be confirmed.

A major concern in the evaluation of individual congeners is the lack of adjustment for other members of the family, which might alter the results because of collinearity. As suggested by Holford et al. (2000) the studies of PCBs congeners and health require an in-depth statistical analysis, in order to untangle the complex relationships that stem from the phenomenon of collinearity.

Most negative studies (Unger et al., 1984; Mussalorauhamaa et al., 1990; Wolff et al., 1993, 2000a,b; Krieger et al., 1994; Hunter et al., 1997; Aschengrau et al., 1998; Hoyer et al., 1998, 2000; Liljegren et al., 1998; Moysich et al., 1998; Helzlsouer et al., 1999; Aronson et al., 2000), including the one at hand, have evaluated PCB levels as the sum of individual congeners or as the concentration relative to a commercial PCB mixture (i.e. Aroclor 1248, 1254 or 1260). Nevertheless, the types of PCBs congeners are not necessarily the same throughout different study populations. The congener structure in complex mixtures determines in turn the resulting oestrogenic activity (Wolff and Toniolo, 1995). Thus, misclassification of the exposure might be sufficient explanation for the lack of an association between PCBs and breast cancer.

In this context, the potential role of PCBs in breast cancer aetiology deserves more detailed attention. Future research should put emphasis on improving the comparability of studies looking at the consequences of human exposure to PCBs.

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