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Polychlorinated biphenyls (PCBs) exposure and cardiovascular, endocrine and metabolic diseases: A population-based cohort study in a North Italian highly polluted area

Elena Raffetti[a], Francesco Donato[b], Fabrizio Speziani[a], Carmelo Scarcella[a], Alice Gaia[c], Michele Magoni[a,*]

[a] ATS Brescia (Brescia Health Protection Agency), Brescia, Italy
[b] Department of Medical and Surgical Specialties Radiological Sciences and Public Health, Unit of Hygiene, Epidemiology, and Public Health, University of Brescia, Italy
[c] Department of Medical and Surgical Specialties Radiological Sciences and Public Health, Institute of Occupational Health and Industrial Hygiene, University of Brescia, Italy

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ABSTRACT

Background and aims: Exposure to polychlorinated biphenyls (PCBs) has been linked to the onset of cardiovascular, endocrine, and metabolic diseases, but no conclusive evidence has been provided so far. A chemical factory produced PCBs from 1938 to 1984 in Brescia (North Italy) resulting in environmental contamination and human exposure. We aimed to evaluate the association between PCB serum levels and subsequent incidence of chronic diseases through a prospective cohort study design.

Methods: Based on surveys conducted in Brescia province between 2001 and 2013, a cohort of 1331 subjects with at least one measure of PCB serum levels during the period was selected and followed longitudinally. Serum concentration of total PCBs was computed summing up the levels of 24 PCB congeners determined by gas chromatography. The data on incidence of hypertension, cardiovascular diseases, and endocrine and metabolic chronic diseases were retrieved from the Brescia Health Protection Agency database. Poisson regression models adjusted for age, level of education, BMI, cholesterol level, tobacco smoking and alcohol drinking were employed to calculate rate ratios (RRs).

Results: 1331 subjects were enrolled (45.7% males, mean age 50.6 years) contributing to 10,006 person-years of follow-up. A dose-response relationship was observed between PCB serum levels and the onset of hypertension (RR for 2nd and 3rd tertiles of serum PCB distribution: 2.07, 95% CI 1.18–3.63, and 2.41, 1.30–4.47, respectively). A possible, though not statistically significant, increase of the risk of cardiovascular disease was also found (RR for 2nd and 3rd tertiles of serum PCB distribution: 1.61, 0.72–3.64, and 1.96, 0.86–4.48, respectively). The results based on lipid-standardized PCBs were slightly attenuated. No association was found between PCB serum levels and occurrence of diabetes and endocrine disorders. Stratified analysis by body mass index showed an increased risk of hypertension in subjects at 2nd and 3rd tertile of serum PCB distribution in overweight/obese subjects only.

Conclusions: These results suggest that PCBs might play a role in the development of hypertension and possibly cardiovascular disease, though alternative explanations are to be considered too.

1. Introduction

Polychlorinated biphenyls (PCBs) are mixtures of up to 209 different organic chlorine compounds. They are included among persistent organic pollutants (POPs) and have been widely dispersed in the environment for decades (IARC, 2016). These hydrophobic and lipophilic compounds are highly resistant to metabolism in vertebrate species, accumulating in the food chain. After ceasing PCB production in most countries by the end of the 1970s or early 1980s, PCB contamination has decreased in both human beings and environment (Consonni et al., 2012; Raffetti et al., 2017).

PCBs have been classified as “carcinogenic to humans” (group 1) by the International Agency for Research on Cancer (IARC) (IARC, 2016), while the association with other chronic diseases is still debated.

* Corresponding author at: Epidemiological Unit of Brescia Agency for Health Protection (ATS Brescia), Viale Duca degli Abruzzi, 15, 25124 Brescia, Italy.
E-mail address: michele.magoni@ats-brescia.it (M. Magoni).

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Experimental findings from animal and human cell system studies showed that PCBs can cause endothelial and endocrine cell dysfunction, hypertension, hyperlipidemia, as well as cerebral cortex under-development (Hennig et al., 2005; Lind et al., 2004; Naveau et al., 2014; Toborek et al., 1995). In the United States general population, the large-scale National Health and Nutrition Examination Survey (NHANES) found increasing prevalence of hypertension, insulin resistance and diabetes with increasing PCB serum values (Ha et al., 2009; Hofe et al., 2014; Lee et al., 2007). In the Swedish general population, PCB dietary exposure was also associated with a higher risk of stroke and myocardial infarction (Bergkvist et al., 2014; Bergkvist et al., 2015; Bergkvist et al., 2016; Kippler et al., 2016). Similar findings were observed in a PCB highly exposed US population: the Anniston Community Health Survey found a relationship between PCB exposure and the prevalence of diabetes (Silverstone et al., 2012) and systolic and diastolic hypertension (Goncharov et al., 2010) though no association with metabolic syndrome (Rosenbaum et al., 2017). However, no PCB blood pressure association was confirmed in subjects with PCB levels persistently high in the Yusho cohort who experienced PCB poisoning (Akagi and Okumura, 1985).

Various PCB congeners are able to interfere with the hormonal system and therefore have been classified among the “endocrine disruptors” (WHO, 2002). Indeed, some studies found that exposure to PCBs may be related with endocrine hormone disruption and neurodevelopmental deficits. In rats, prenatal exposure to PCBs may alter the thyroid status and the cerebral cortex development (Kobayashi et al., 2008; Naveau et al., 2014). In humans, PCB serum levels was linked to obesity, women's menstrual cycles disorders, and alteration in triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone receptor antibodies (TSHRab) in some studies (Dirinck et al., 2011; Gallo et al., 2016; Gaum et al., 2016).

However, these studies have some weaknesses: the NHANES and Anniston Community Health Survey have a cross-sectional design while the Swedish study estimated PCB serum intake only indirectly, from food frequency questionnaires. Longitudinal studies with biologic measures of PCB body burden (exposure) and a valid system for detection of incidence cases (outcome) are necessary for providing evidence of a causal relationship between PCB exposure and occurrence of chronic diseases.

A chemical factory produced PCBs and other organochlorines in an industrialized town in North Italy, leading to a heavy PCB pollution of the environment and resident population (Donato et al., 2006; Turrio-Baldassarri et al., 2007). However, a cross-sectional investigation found no evidence of association between PCB exposure and thyroid disorders and diabetes (Donato et al., 2008; Zani et al., 2013). We aimed to assess the association between PCB serum level and incidence of chronic diseases by a population-based prospective cohort study.

2. Methods

2.1. Setting and population

A chemical factory (Caffaro) located in Brescia, a highly industrialized town with about 200,000 inhabitants in Northern Italy, produced PCBs from 1938, with a total of 28,900 tons between 1955 and 1984 (De Voogt and Brinkman, 1989). PCB contamination was found in the soil of an area of the town, and in locally produced food, especially animal products with a reducing gradient getting far from the factory (Donato et al., 2006; Turrio-Baldassarri et al., 2007). One investigation on a random sample of 527 adults living in the town was carried out in 2003, showing 5- to 10-fold higher mean of total PCB serum concentration than those found in unexposed populations in developed countries (Apostoli et al., 2005; Donato et al., 2006; Turrio-Baldassarri et al., 2007). In 2013–2014 the survey was repeated with the same methods in Brescia and two neighboring villages, including a total of 814 adults (Magoni et al., 2016). All subjects who had at least one measure of their PCB serum levels between 2003 and 2014 were included in the present cohort study and followed prospectively.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from all subjects. The study protocol was approved by the local Ethic Committee of Brescia Province.

2.2. PCB measurements

PCB serum levels were measured in 1331 subjects at the enrollment in the cohort study, between 2003 and 2014. For subjects with more measures during the period, only the first one (baseline) was considered. To this end, a 20 ml blood sample under fasting conditions was taken for each subject. > 90% subjects underwent an interview with a questionnaire on their occupational and environmental exposures. The serum concentration of 24 PCB congeners was determined according to the International Union of Pure and Applied Chemistry (IUPAC) abbreviated nomenclature (Mills et al., 2007): 28, 31, 52, 77, 81, 101, 105, 114, 118, 123, 126, 128, 138, 153, 156, 157, 167, 169, 170, 180, 189, 194, 206 and 209. PCBs were measured using a Hewlett-Packard 6890N gas chromatograph coupled with an MSD HP 5973. Analytical procedure, limit of quantification and method accuracy assessment were reported in a previous study (Apostoli et al., 2005). All the PCB analyses were performed at the Laboratory of Occupational Hygiene and Toxicology of the University of Brescia, Italy. Total PCB concentration was determined by summing up the concentration of the PCB congeners detected.

2.3. Follow-up

For each subject, the first PCB serum measure defined the date of enrollment in the cohort and the start of the follow-up, which lasted up to 31th December 2016 or loss to observation or death (99.2% had a complete follow-up).

2.4. Outcome

The outcomes were and incidence rates of hypertension, cardiovascular diseases, diabetes, endocrine diseases and thyroid disorders. Some of the thyroid disorders were also included in endocrine diseases. These diseases were chosen on a priori list based on scientific evidence of diseases possibly associated with PCB exposure. We retrieved the data on the diseases of interest from the Brescia Health Protection Agency database (Lonati et al., 2008). This database integrates the information from all the health services provided by the National Health Service for each individual of the resident population. Each case of chronic disease was identified according to one or more of the following criteria (Table 1): (i) use of in-hospital or out-patient services with an ICD9-CM code; (ii) medicine prescription, (iii) ticket exemption for disease care; (iv) admission to a residential care or psychiatric facility.

Prevalent cases were excluded from the analysis of incidence rates for each disease.

2.5. Other variables

In order to adjust for potential confounding from lifestyle and clinical risk factors for chronic diseases, we collected data on Body Mass Index (BMI), total cholesterol levels, smoking habits, alcohol consumption and education for each subject. BMI was computed as the ratio of weight in kilograms to height in meters squared and categorized as underweight, normal, overweight and obesity. According to tobacco use, subjects were categorized as current, former and never smokers. Daily alcohol consumption was assessed in g/day summing up the consumption of wine, beer, and spirits according to their alcohol content, and dichotomized into high or low according to the Italian/WHO