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Serum organochlorines and non-Hodgkin lymphoma: A case-control study in Israeli Jews and palestinians

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HIGHLIGHTS

- Organochlorine serum values were higher in Israeli Jews than in Palestinian Arabs.
- Organochlorine exposure in Israel was comparable with other high-income countries.
- High-chlorinated PCBs were associated with non-Hodgkin lymphoma.

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ABSTRACT

Associations of organochlorine (OC) pesticides and polychlorinated biphenyls (PCBs) with non-Hodgkin lymphoma are controversial. We compared serum levels of 6 OC pesticides and 38 PCBs in Israeli Jews (IJ) and Palestinian Arabs (PA) and assessed possible associations with B-cell non-Hodgkin lymphoma (B-NHL). Ninety B-NHL cases (50 IJ and 40 PA) and 120 controls (65 IJ and 55 PA) were included. Median concentrations of analytes in controls were compared across ethnic groups using quantile regression, adjusting for age and sex. We used logistic regression to derive odds ratios (OR) and 95% confidence intervals (CI) for detectable analytes and B-NHL, adjusting for age, ethnic group, faming and body mass index. Median values of PCBs and dichlorodiphenyldichloroethylene (DDE) were higher in IJ vs PA controls ($P = 0.0007$), as were several PCBs (74, 99, 118, 138, 146, 153, 156, 163, 170, and 180). Overall, OC pesticide and PCB exposures were comparable with reports from high-income countries. B-NHL was associated with PCB 146 (OR 1.70, 95% CI: 1.02, 2.83), PCB 156 (OR 1.75, 95% CI: 1.06, 2.89), and high-chlorinated PCBs (OR 1.55, 95% CI: 1.00, 2.40) in all study subjects. These associations were robust in quantile as well as sensitivity analyses. An association of DDE with B-NHL was noted in PA (OR 1.72, 95% CI: 1.07, 2.77), but not in IJ (OR 0.87, 95% CI: 0.59, 1.27). Although high-chlorinated PCB concentrations did not indicate high exposure levels, our findings indicate that B-NHL may be associated with this exposure.

1. Introduction

The age-standardized rates of non-Hodgkin lymphoma (NHL) in Israel were the highest worldwide as recorded in GLOBOCAN 2012 in men and women alike, while those for all cancer were in the

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lowest quintile (IARC, 2012). However, the incidence of NHL in closely-residing Palestinian Arabs (PA) is less well measured but is likely lower given rates in the Jordanian population (Anton-Culver et al., 2016). Notwithstanding, marked increases in the incidence of NHL in Israeli Jews (IJ) up to 2000 imply environmental exposures as causal factors.

Associations of serum or plasma concentrations of organochlorine (OC) pesticides and polychlorinated biphenyls (PCBs), OC chemicals used in various industries, with the risk of NHL are controversial. While many reports have shown increased risk with OC exposure (Rothman et al., 1997; De Roos et al., 2005; Engel et al., 2007; Colt et al., 2009; Freeman and Kohles, 2012), others have shown no association (Cocco et al., 2008; Laden et al., 2010; Kelly et al., 2017; Zani et al., 2017). In Israel, OC pesticides like dichlorodiphenyltrichloroethane (DDT) were in extensive use in the 1960s and 1970s (Richter and Safi, 1997). Indeed, high levels of p,p-dichlorodiphenyldichloroethylene (DDE), a DDT metabolite, were found in adipose tissue of autopsied Israelis who died of trauma in 1984–1988 (Ben-Michael et al., 1999). PA residing in the West Bank share the same ecosystem with Israelis, although they differ in terms of culture, diet, income, urban/rural residence, and other exposures. Further, the use of banned OC pesticides like DDT persisted in the West Bank at least into the late 1990s (Issa et al., 2010). In the Israeli population, levels of DDT, DDE and PCBs in human milk were reported to be comparable to those in other Western countries (Wasser et al., 2015). However, milk-serum correlation for pesticides and PCBs is far from perfect (LaKind et al., 2009), and OC pesticides persist in serum more than three decades following a ban on their use (Saoudi et al., 2014).

To our knowledge, no serum monitoring of OC pesticides and PCBs has been conducted in healthy Israeli Jews (IJ) since 1986 (Pines et al., 1987) and no reports are available on serum levels in healthy PA (Richter and Safi, 1997). Thus, we aimed to both quantify these persistent pollutants in serum of both IJ and PA, and to assess their association with B-NHL.

2. Methods

2.1. Study population

This exploratory study was part of a larger community and hospital-based case-control study in Israel and the West Bank. Details on the parent study design have been published elsewhere (Kleinstern et al., 2016, 2017). Briefly, the study was conducted between 2009 and 2014 in Hadassah-Hebrew University Medical Center in Jerusalem, Israel; participating centers in the West Bank were Augusta Victoria Hospital (East Jerusalem), Al-Watani Hospital (Nablus), and Al-Hussein Hospital (Beit Jala). Eligible cases were 18 years and older with pathologically confirmed B-cell NHL (B-NHL) and no known HIV infection. The parent study population included 930 IJ (516 cases and 414 controls) and 701 PA (307 cases and 394 controls). Participation rate among cases was ≥95%, and they were recruited as soon as possible after histologic diagnosis, with 80% of interviews and sampling within 1.5 years (Kleinstern et al., 2017). Given budget considerations a subsample of the entire study population was selected for assessment of OC levels based on the following criteria: adequate serum volume and cases with serum samples <30 days after the first administration of chemotherapy, as organochlorine levels have been shown to decrease during treatment for NHL (Baris et al., 2000).

Controls were recruited among adults who accompanied cases to their care in treating centers or attended 13 walk-in clinics across the West Bank, and were frequency-matched by age and sex in every study site. Controls with a history of cancer were excluded. Israeli cases and controls included in this analysis are those whose self-reported religion was Jewish, to allow the comparison of populations with distinct ancestries and culture. In order to assess the possible influence of agricultural exposures on OC levels in the population we included for each ethnic group a minimum of 15 controls who reported that they had worked in agriculture. Of the 65 IJ controls in this study, 3% were unrelated family members (daughter- or son-in-law) of cases, and 24% were spouses of other cases in the parent study. Of 55 PA controls, none were spouses or family members of cases. The study was approved by the institutional review boards of the Hadassah University Hospital in Jerusalem, Israel, and of the Palestinian Ministry of Health. All participants gave written informed consent.

All study participants were interviewed in person and in their native tongue by a trained interviewer. We used a structured questionnaire based on the European Epilymph study (Besson et al., 2006) to obtain data on educational background and self-reported religion, occupational background, place of residence, lifestyle factors, hobbies, exposures and medical history.

2.2. Serum samples and laboratory analysis

Blood samples were drawn in non-fasting state between 2009 and 2014. They were immediately processed and separated into plasma, red blood cells and buffy coat. After separation, samples were transferred to two 1 ml aliquots and immediately frozen to −80° Celsius. In 2015, samples from 90 cases and 120 controls were shipped in 1 ml aliquots to the Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine (IPASUM) of the University of Erlangen-Nuremberg, Germany. Measurements of 38 PCB congeners (Congener numbers (Ballschmiter and Zell, 1980): 18, 20, 28, 31, 49, 51, 66, 69, 74, 77, 81, 99, 101, 105, 114, 118, 123, 126, 138, 146, 149, 153, 156, 157, 166, 167, 169, 170, 178 180, 182, 183, 187, 189, 190, 196, 198, and 203) were performed using the isotope-dilution gas chromatography-mass spectrometry method as previously described (Meyer et al., 2013). Measurements of 6 OC pesticides (DDT, DDE, β-hexachlorocyclohexane [β-HCH], α-HCH, hexachlorobenzene [HCB], and γ-HCH [lindane]) were performed using gas chromatography coupled with an electron-capture detector as previously described (Saoudi et al., 2014). The methods utilized in IPASUM have been externally validated in the German External Quality Assessment Scheme (Göen et al., 2012). The limit of detection (LOD) for HCH compounds was 0.01 μg/L, and 0.001 μg/L for all other analytes.

2.3. Statistical analysis

Descriptive statistics were used to capture patient demographics, as well as height in centimeters, weight in kilograms, residence location (urban, rural, or unknown), education (0–8, 9–12, >12 years, or unknown), farming (ever vs never occupation in agriculture), smoking (ever vs never) and year of sample collection. Self-reported consumption of fruits, vegetables, meat/poultry, fish, milk and dairy products was quantified as frequency per week. Food consumption frequencies of IJ and PA subjects were compared using a Mantel-Haenszel Chi-Square test.

Undetectable analyte values were filled in as LOD/$\sqrt{2}$ (Hornung and Reed, 1990). Median concentrations of analytes in PA vs IJ controls as well as in controls with and without (including unknown) history of farming were compared using quantile regression models and adjusting for age and sex. The relations between analytes with >70% detection were explored using Spearman correlation coefficient. Associations between B-NHL and analytes with ≥70% detection rates in serum were determined after natural-log transformation of the analytes (Colt et al., 2009), while analytes

with <70% detection were excluded from these analyses. We used unconditional logistic regression models to assess the odds ratios (ORs) and 95% confidence intervals (CI) for the associations of B-NHL with a single-unit increase in the log-transformed analyte, expressed in μg/L. In primary analyses, these associations were determined in all study subjects. Grouped PCB congeners were also treated as continuous variables. Four groups were considered: low-chlorinated (74, 99, and 118), dioxin-like (118 and 156), high-chlorinated (138, 146, 153, 156, 163, 170, 180, 183 and 187), and total PCBs. Each group comprised the sum of molar concentrations of each individual PCB (Spector et al., 2014). We coded each exposure category based on tertiles in controls (De Roos et al., 2005). We then fitted a logistic regression for the association of tertiles of exposure and B-NHL, where the independent variable was one tertile increase in PCB category.

We also assessed exposures as categorical variables, by classifying each analyte as quartiles of exposure in the entire study population (Spinelli et al., 2007). For each analyte, we determined the OR for B-NHL comparing each quartile with quartile 1. We assessed the trend in associations modeling quartiles as a continuous variable and using a chi-square test. We applied the same method to summed PCBs.

A change-in-estimate approach was used for variable selection. Due to sample size and crude effect size, we chose a cutoff of 5% for confounder identification (Lee, 2014). The full model contained age, sex, ethnic group, BMI, education, smoking, and farming. Residence was left out *a priori* due to the differential nature of missing values. The removal of smoking, sex, and education led to changes in estimate around 1%, leading to a final model that included age, ethnic group, BMI, and farming.

To explore possible effect modification by B-NHL sub-type, we repeated the analyses after re-classifying cases by diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and other types, predominantly marginal zone lymphoma. To assess various differences in associations of OC and B-NHL across ethnic groups, we conducted separate analyses in IJ and PA. We also assessed for effect modification by ethnic group by introducing at as an interaction term in the analytic model. To assess for information bias in cases, we restricted our analyses to cases whose samples were drawn at the date of B-NHL diagnosis. Finally, to address possible selection bias, we repeated the analyses after excluding any study subject with a history of farming. All analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Study population

The study population comprised 115 IJ (50 cases and 65 controls) and 95 PA (40 cases and 55 controls). The median age of study participants was around 60 years with a slight imbalance between PA cases and controls (Table 1). IJ participants reported a predominantly urban residence, while most PA cases and controls were from rural areas. More IJ study subjects had ever smoked and had obtained post-secondary education, while PA subjects more frequently reported agriculture as their previous or current occupation. More PA subjects were recruited in 2009–2010, whereas more IJ participants were enrolled in 2011–2014. Among IJ cases (62%) and controls (66%), there was a predominance of Ashkenazi Jews.

Food consumption habits among study participants are detailed in Table S1 in the Supplementary Material. A higher consumption of

Table 1
General characteristics of the study population, $n = 210$.

Characteristic	Israeli Jews		Palestinian Arabs	
	Cases ($n = 50$)	Controls ($n = 65$)	Cases ($n = 40$)	Controls ($n = 55$)
Age (years) [median (range)]	59 (21–91)	61 (23–86)	56 (18–80)	62 (18–92)
Male sex [*n* (%)]	32 (64)	41 (63)	20 (50)	25 (46)
Height (cm) [median (range)]	170 (146–186)	169 (149–195)	165 (121–190)	169.5 (144–187)
Weight (kg) [median (range)]	78 (50–140)	75 (40–114)	80 (46–105)	73.5 (40–140)
Residence type [*n* (%)]				
Urban	46 (92)	49 (75)	8 (20)	1 (2)
Rural	4 (8)	16 (25)	20 (50)	33 (60)
Unknown	0 (0)	0 (0)	12 (30)	21 (38)
Education (years) [*n* (%)]				
0–8	3 (6)	0 (0)	19 (48)	38 (69)
9–12	10 (20)	17 (26)	14 (35)	6 (11)
≥13	37 (74)	43 (74)	6 (15)	10 (18)
Unknown	0 (0)	0 (0)	1 (3)	1 (2)
Farming [*n* (%)]	3 (6)	15 (23)	11 (28)	21 (38)
Year of sample collection [*n* (%)]				
2009	0 (0)	0 (0)	3 (8)	11 (20)
2010	4 (8)	10 (15)	4 (10)	4 (7)
2011	12 (24)	26 (40)	18 (45)	39 (71)
2012	21 (42)	20 (31)	11 (28)	1 (2)
2013	11 (22)	5 (8)	4 (10)	0 (0)
2014	2 (4)	4 (6)	0 (0)	0 (0)
Smoking [*n* (%)]				
Ever smoked	26 (52.0)	33 (50.8)	14 (35.0)	18 (32.7)
Never smoked	24 (48.0)	32 (49.2)	26 (65.0)	37 (67.3)
Non-Hodgkin lymphoma type [*n* (%)]				
Diffuse large B-cell lymphoma	26 (52)		30 (75)	
Follicular	11 (22)		6 (15)	
Other	13 (26)		4 (10)	
Time from diagnosis (months) [median (range)] to sample collection	0 (0–30)		1 (0–2)	
Initial treatment [n (%)]				
Chemoimmunotherapy	35 (70)		22 (55)	
Watchful waiting	4 (8)		0 (0)	
Other	11 (22)		18 (45)	

fruits, vegetables, meat/poultry, fish, milk, and dairy products was noted among IJ subjects compared with PA subjects.

3.2. Assessment of OC and PCB analytes

The disposition of all tested analytes is presented in Fig. 1 and Table S1 in the Supplementary Material. Overall, two OC pesticides and 12 PCB congeners were detected above 70%, comprising 31.8% of analytes measured. Adjusted median concentrations of DDE were 1.29 μg/L (95% CI: 0.55–2.03) higher in IJ vs PA controls ($P = 0.0007$). In IJ controls, DDT was detected in 12/65 (18.5%), whereas in PA controls it was detected in 30/55 (54.5%), but there was no notable difference in adjusted medians. Among PCB congeners, PCB 74, PCB 99, PCB 118, PCB 138, PCB 146, PCB 153, PCB 156, PCB 163, PCB 170, and PCB 180 were detected in higher levels in IJ vs PA controls. There were no differences in median concentrations of any of the analytes between controls with and without a history of farming (Table S2, Supplementary Material). Notably, there was a strong correlation between all analytes (Table S3, Supplementary Material).

3.2.1. Associations of OC and PCB analytes with B-NHL

Associations of log-transformed OC with B-NHL in all study subjects are presented in Table 2. Neither DDE nor HCB levels were associated with B-NHL. However, PCB 146 (OR 1.70, 95% CI: 1.02, 2.83) and PCB 156 (OR 1.75, 95% CI: 1.06, 2.89) were associated with B-NHL as single analytes. Among grouped PCBs, high-chlorinated PCBs were associated with B-NHL (OR 1.55, 95% CI: 1.00, 2.40). Associations of OC by quartiles and B-NHL are presented in Table 3. Heterogeneity across quartiles was noted in the associations of PCB 138, 146, and 153 as single analytes; similarly, there was heterogeneity between quartiles of high-chlorinated and total PCBs.

3.3. Associations across ethnic groups and B-NHL subtypes

Associations of OC and PCB analytes with B-NHL in IJ and PA separately are presented in Table 4. Notably, DDE was associated with B-NHL in PA (OR 1.72, 95% CI: 1.07, 2.77) and not IJ (OR 0.87, 95% CI: 0.59, 1.27). Similarly, PCB 156 was associated with B-NHL in PA (OR 3.31, 95% CI: 1.31, 8.39), but in IJ (OR 1.07, 95% CI: 0.56, 2.05). However, when we introduced ethnic group as an interaction term in these associations, there was no significant effect modification ($P = 0.29$ and $P = 0.68$ for DDE and PCB 156, respectively).

Overall, associations of PCB 146, PCB 156, and high-chlorinated PCB with B-NHL were of similar magnitude across B-NHL subtypes; however, none reached statistical significance (Table S4, Supplementary Material).

In sensitivity analyses, exclusion of cases with pretreatment for B-NHL led to consistent associations, although none was statistically significant (Table S5, Supplementary Material). Similarly, the exclusion of study subjects with a history of agricultural occupation led to positive associations of high-chlorinated PCB and B-NHL whose CI overlapped with primary analysis (Table S6, Supplementary Material).

4. Discussion

The present small study is to our knowledge, the first to explore possible associations of OC exposures and NHL in Israelis and Palestinians (geographically proximate but highly distinct populations residing mainly in urban and rural settings, respectively). We found higher levels of the banned OC pesticides DDT and β-HCH in PA vs IJ controls, while the opposite was true for DDE. High-chlorinated PCB were associated with B-NHL using two classification systems.

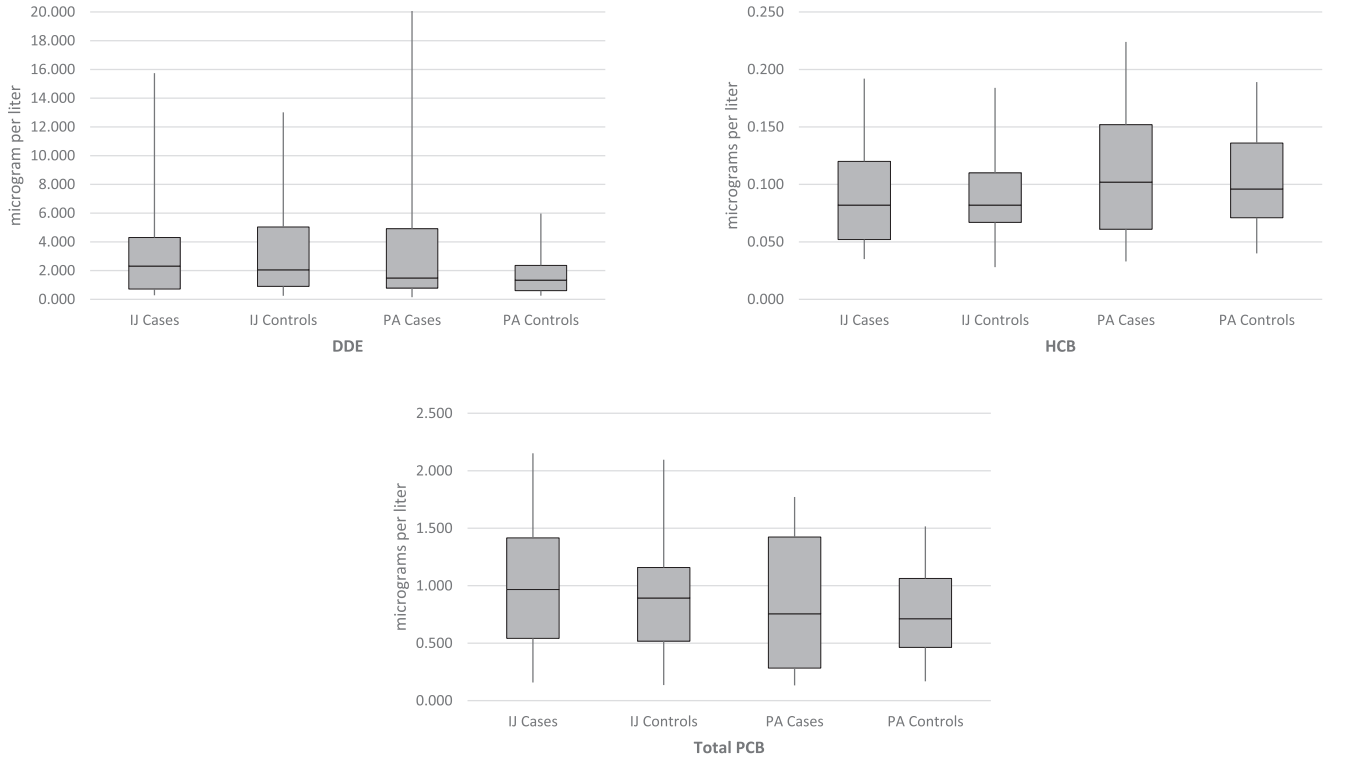

Fig. 1. Distribution of serum concentrations for p,p-dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), and the total polychlorinated biphenyls (PCB). Values are presented as box plots with median values, quartiles 1 and 3, and error bars to the 5th and 95th percentiles.

Table 2
Associations between log-transformed organochlorine exposures and non-Hodgkin lymphoma in all study subjects.

Exposure	Adjusted OR (95% CI)[a]
DDE	1.15 (0.87, 1.52)
HCB	1.06 (0.58, 1.96)
PCB 74	1.00 (0.65, 1.55)
PCB 99	1.30 (0.83, 2.03)
PCB 118	1.16 (0.74, 1.82)
PCB 138	1.43 (0.95, 2.16)
PCB 146	**1.70 (1.02, 2.83)**
PCB 153	1.28 (0.83, 1.97)
PCB 156	**1.75 (1.06, 2.89)**
PCB 163	1.26 (0.80, 1.99)
PCB 170	1.19 (0.77, 1.85)
PCB 180	1.25 (0.81, 1.93)
PCB 183	1.38 (0.86, 2.23)
PCB 187	1.25 (0.84, 1.89)
Low-chlorinated PCB[b]	1.06 (0.71, 1.60)
High-chlorinated PCB[c]	**1.55 (1.00, 2.40)**
Dioxin-like PCB[d]	1.17 (0.77, 1.79)
Total PCB	1.45 (0.95, 2.23)

Abbreviations; BMI, body mass index; CI, confidence intervals; DDE, Dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; OR, odds ratio; PCB, polychlorinated biphenyls.
[a] Adjusted for age (continuous), ethnic group, farming and body mass index.
[b] PCB 74, 99, and 118.
[c] PCB 138, 146, 153, 156, 163, 170, 180, 183 and 187.
[d] PCB 118 and 156.

Table 3
Associations between quartiles of organochlorine exposures and non-Hodgkin lymphoma in all study subjects.

Exposure	Adjusted OR (95% CI)[a]	P for trend[b]
DDE		
Q1 (≤0.772)	Ref	
Q2 (0.773–1.684)	0.97 (0.40, 2.36)	
Q3 (1.684–3.697)	1.17 (0.47, 2.89)	
Q4 (>3.697)	1.78 (0.67, 4.77)	0.28
HCB		
Q1 (≤0.063)	Ref	
Q2 (0.064–0.088)	0.68 (0.28, 1.69)	
Q3 (0.088–0.126)	0.85 (0.33, 2.15)	
Q4 (>0.126)	0.92 (0.37, 2.27)	0.99
PCB 74		
Q1 (≤0.019)	Ref	
Q2 (0.020–0.032)	1.10 (0.46, 2.63)	
Q3 (0.032–0.056)	0.87 (0.33, 2.32)	
Q4 (>0.056)	1.19 (0.45, 3.17)	0.88
PCB 99		
Q1 (≤0.012)	Ref	
Q2 (0.013–0.020)	1.20 (0.50, 2.90)	
Q3 (0.020–0.033)	0.73 (0.29, 1.80)	
Q4 (>0.033)	1.61 (0.66, 3.90)	0.49
PCB 118		
Q1 (≤0.024)	Ref	
Q2 (0.025–0.042)	0.84 (0.33, 2.13)	
Q3 (0.043–0.073)	0.82 (0.30, 2.22)	
Q4 (>0.073)	1.39 (0.53, 3.69)	0.44
PCB 138		
Q1 (≤0.047)	Ref	
Q2 (0.048–0.094)	0.60 (0.23, 1.60)	
Q3 (0.095–0.149)	0.92 (0.35, 4.37)	
Q4 (>0.149)	**2.87 (1.11, 7.38)**	**0.02**
PCB 146		
Q1 (≤0.011)	Ref	
Q2 (0.012–0.023)	0.52 (0.21, 1.28)	
Q3 (0.024–0.034)	1.60 (0.59, 3.97	
Q4 (>0.034)	2.58 (0.93, 7.18)	**0.02**
PCB 153		
Q1 (≤0.120)	Ref	
Q2 (0.121–0.208)	1.12 (0.44, 2.87)	
Q3 (0.209–0.312)	0.93 (0.35, 2.45)	
Q4 (>0.312)	**3.24 (1.19, 8.86)**	**0.03**
PCB 156		
Q1 (≤0.012)	Ref	
Q2 (0.013–0.024)	0.86 0.33, 2.21)	
Q3 (0.025–0.038)	1.34 (0.49, 3.67)	
Q4 (>0.038)	2.90 (0.99, 8.49)	**0.04**
PCB 163		
Q1 (≤0.019)	Ref	
Q2 (0.020–0.035)	0.53 (0.23, 1.34)	
Q3 (0.036–0.053)	1.28 (0.49, 3.34)	
Q4 (>0.053)	1.71 (0.62, 4.71)	0.11
PCB 170		
Q1 (≤0.034)	Ref	
Q2 (0.035–0.062)	0.92 (0.36, 2.37)	
Q3 (0.063–0.086)	1.72 (0.62, 4.80)	
Q4 (>0.086)	1.62 (0.57, 4.61)	0.26
PCB 180		
Q1 (≤0.098)	Ref	
Q2 (0.099–0.187)	0.55 (0.21, 1.46)	
Q3 (0.188–0.274)	1.25 (0.45, 3.47)	
Q4 (>0.274)	2.03 (0.69, 6.00)	0.06
PCB 183		
Q1 (≤0.007)	Ref	
Q2 (0.008–0.017)	0.78 (0.30, 2.02)	
Q3 (0.018–0.027)	0.65 (0.26, 1.61)	
Q4 (>0.027)	1.80 (0.75, 4.33)	0.29
PCB 187		
Q1 (≤0.026)	Ref	
Q2 (0.027–0.051	0.91 (0.36, 2.29)	
Q3 (0.052–0.079)	1.23 (0.45, 3.32)	
Q4 (>0.079)	2.34 (0.89, 6.18)	0.06
Low-chlorinated PCB		
Q1 (≤0.056)	Ref	
Q2 (0.057–0.101)	0.78 (0.32–1.89)	
Q3 (0.102–0.161)	0.62 (0.25–1.57)	
Q4 (>0.161)	1.21 (0.49–3.02)	0.78
High-chlorinated PCB		
Q1 (≤0.410)	Ref	
Q2 (0.402–0.707)	0.56 (0.22–1.52)	
Q3 (0.708–1.046)	1.01 (0.38–2.69)	
Q4 (>1.046)	2.60 (0.93–7.23)	**0.03**
Dioxin-line PCB		
Q1 (≤0.039)	Ref	
Q2 (0.039–0.068)	0.37 (0.14–1.00)	
Q3 (0.069–0.110)	0.72 (0.28–1.87)	
Q4 (>1.110)	1.08 (0.42–2.79)	0.49
Total PCB		
Q1 (≤0.463)	Ref	
Q2 (0.464–0.826)	0.90 (0.35–2.31)	
Q3 (0.827–1.196)	1.00 (0.38–2.61)	
Q4 (>1.196)	2.78 (1.00–7.75)	**0.045**

Abbreviations: CI, confidence intervals; DDE, Dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; OR, odds ratio; PCB, polychlorinated biphenyls.
[a] Adjusted for age (continuous), ethnic group, farming and body mass index.
[b] Wald Chi-square test modeling quartiles as a continuous variable.

4.1. OC pesticides and B-NHL: possible health implications

A study of elderly Swedish men and women reported comparable wet-weight levels of DDE to those found herein in IJ controls, while higher than in PA controls (Stubleski et al., 2018). Studies from polluted areas in Brazil and Mexico reported serum concentrations of OC pesticides which were four-fold and twice higher than in both IJ and PA controls in our study, respectively (Waliszewski et al., 2012; Freire et al., 2014). These comparisons suggest OC pesticide exposure among PA is not consistent with high pollution levels despite previous reports on pesticide use. We detected DDT in 61.1% of PA subjects, and the median (interquartile range) of DDT/DDE ratio in this population was 1.9% (0.8–3.7%), which may suggest past rather than recent use of DDT (Ahlborg et al., 1995). These findings are aligned with data from the

Table 4
Associations between organochlorine exposures and non-Hodgkin lymphoma stratified by ethnic group.

Exposure	Israeli Jews	Palestinian Arabs
	Adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[a]
DDE	0.87 (0.59, 1.27)	**1.72 (1.07, 2.77)**
HCB	0.93 (0.42, 2.07)	1.85 (0.63, 5.41)
PCB 74	0.82 (0.44, 1.52)	1.23 (0.64, 2.36)
PCB 99	1.07 (0.62, 1.87)	1.99 (0.86, 4.63)
PCB 118	0.91 (0.50, 1.66)	1.99 (0.92, 4.29)
PCB 138	1.18 (0.69, 2.02)	1.79 (0.88, 3.63)
PCB 146	1.31 (0.67, 2.54)	2.08 (0.86, 5.02)
PCB 153	0.96 (0.54, 1.71)	1.66 (0.82, 3.37)
PCB 156	1.07 (0.56, 2.05)	**3.31 (1.31, 8.39)**
PCB 163	0.88 (0.48, 1.61)	1.83 (0.83, 4.05)
PCB 170	0.77 (0.41, 1.46)	1.62 (0.82, 3.19)
PCB 180	0.97 (0.52, 1.79)	1.36 (0.69, 2.67)
PCB 183	1.26 (0.67, 2.39)	1.38 (0.64, 2.97)
PCB 187	1.05 (0.59, 1.90)	1.26 (0.69, 2.30)
Low-chlorinated PCB[b]	0.86 (0.50, 1.48)	1.56 (0.79, 3.08)
High-chlorinated PCB[c]	1.24 (0.70, 2.25)	1.72 (0.85, 3.51)
Dioxin-like PCB[d]	0.79 (0.44, 1.42)	1.95 (0.97, 3.90)
Total PCB	1.04 (0.59, 1.83)	2.04 (0.97, 4.28)

Abbreviations: CI, confidence intervals; DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; OR, odds ratio; PCB, polychlorinated biphenyl.
[a] Associations are per 1-unit increase in the log-transformed single analytes, adjusted for age (continuous), farming, and body mass index.
[b] PCB 74, 99, and 118.
[c] PCB 138, 146, 153, 156, 163, 170, 180, 183 and 187.
[d] PCB 118 and 156.

eastern Mediterranean basin indicating no new inputs of DDT (Shoham-Frider et al., 2009).

However, we report an association of DDE exposure with B-NHL in PA and not in IJ. On the one hand, this could stem from PA cases being diagnosed later in the course of B-NHL than IJ cases, thus increasing OC concentrations due to disease cachexia. Indeed, late stage diagnoses of cancer in the West Bank have been reported (Abu-Rmeileh et al., 2016) and may drive the positive associations with OC exposure, while only DDE and PCB 156 were statistically significant in PA. On the other hand, metabolic pathways of DDT elimination may be different in PA and IJ. Of note, although median concentrations of DDT did not differ between PA and IJ, adjusted third quartile (75%) concentrations in PA were 0.033 μg/L (95% CI: 0.0.010−0.056) higher than in IJ. Whether this has any significance with regard to B-NHL remains to be determined.

4.2. PCB and B-NHL: possible health implications

The median concentrations of wet-weight PCBs in IJ controls were comparable to those reported in Danish and Swedish study subjects (Meyer et al., 2013; Stubleski et al., 2018) but slightly lower than Dutch subjects for some of the analytes (Dirinck et al., 2016). In PA controls, PCB concentrations were lower than all of these Western European comparison populations, and were comparable with delivering Slovak mothers (Park et al., 2007). Thus, these comparisons point to an overall low exposure to PCB in IJ and PA relative to high-income countries, a consistent finding with country comparisons of human breast milk exposure levels (Wasser et al., 2015). As relates to higher PCB concentrations in IJ subjects compared with PA subjects, it is consistent with higher self-reported consumption of fish, a possible source of high-chlorinated PCB exposure.

Several high-chlorinated PCB − and no low-chlorinated PCB − were associated with B-NHL in pooled analyses. The level of chlorination determines the source of human exposure: low-chlorinated PCB are principally airborne, while high-chlorinated PCB stem from food (Grimm et al., 2015), mainly contaminated fish (Weintraub and Birnbaum, 2008). In the Mediterranean coast, PCB 118 and PCB 126 have been reported to be major contributors to dioxin-like activity, likely due to absorption in fish livers (Yudkovski et al., 2015). In light of possible ties with B-NHL and the high incidence of this disease in Israel, our findings call for closer monitoring of food sources for PCB contamination.

4.3. Comparison with other evaluations

As previously mentioned, the association of high body burden of PCB and NHL is controversial (Freeman and Kohles, 2012; Zani et al., 2017). In particular, associations of individual PCB congeners with NHL have been inconsistent. For example, adjusted OR for PCB 118 range from 0.4 (Cocco et al., 2008) to 5.4 (Engel et al., 2007). Given that exposure occurs primarily as mixed chemicals, (Aroclors), grouped congener exposures can be more readily interpreted as causal, and led to the Environmental Protection Agency 2005 classification of Aroclor 1016 and 1254 as probably carcinogenic (EPA, 2014). The latter mixture contained high percentages of PCB 146, PCB 153, and PCB 156 (ATSDR). Nevertheless, the International Agency for Research on Cancer has concluded in 2016 that dioxin-like PCBs (77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, and 189) are carcinogenic to humans (IARC, 2016). Interestingly, this study is not the first to show that only high-chlorinated PCBs are associated with NHL (De Roos et al., 2005). Thus, pooling inert with truly-oncogenic PCBs may dilute a true effect. Nonetheless, no PCBs in adipose tissue was found to be associated with survival after NHL diagnosis (Roswall et al., 2018). Thus, controversy is expected to continue.

We identified three studies which estimated a specific association of plasma concentrations of PCB 156 with NHL. Two case-control studies that included 600 samples in which these compounds were detected reported positive trends across quartiles and ORs ranging from 1.77 to 2.70 for the highest quartile (De Roos et al., 2005; Spinelli et al., 2007). When PCB highest-percentile associations were meta-analyzed, the OR for PCB 156 was the highest among PCB congeners (Freeman and Kohles, 2012). A further study was a case-control study nested within two European cohorts (Kelly et al., 2017). This study included 140 samples and reported no trend in quartiles and no association of the highest quartile (OR 0.69). In our study, the highest quartile OR for PCB 156 and B-NHL is 2.90 (95% CI: 0.99, 8.49), resembling the higher of these estimates.

Of interest, PCB 146 and PCB 163 were not measured in many studies reporting on serum OC concentrations and B-NHL (Cocco et al., 2008; Laden et al., 2010; Kelly et al., 2017). Only one study reported single-analyte associations for PCB 146 and NHL (De Roos et al., 2005). The quartile 4-vs-1 OR was 1.81 (95% CI: 0.70, 4.64) while no trend was noted across quartiles. In our study the highest quartile OR was 2.58 (95% CI: 0.93, 7.18), and there was a positive trend across quartiles. Our findings thus contribute to the growing evidence that high-chlorinated PCB may be associated with NHL. Nevertheless, we have not shown associations of PCB and B-NHL in IJ alone, and thus causality in this population remains uncertain. Given the expense and effort required to conduct such studies, our findings thus call for further pooling of existing studies.

4.4. Strengths and limitations

The objective assessment of a wide variety of persistent OC pollutants in serum by validated laboratory methods is a major strength of our study. We were also able to study two populations seldom represented in serum biomonitoring studies and explore possible effect modification of the association between OC and B-

NHL in several ways.

Several limitations should be considered. First, our sample size was modest. A post-hoc power calculation leads to a power of 0.80 to detect an OR of 2.30 where quartile 4 (in controls) of exposure is compared with quartile 1 and alpha is 0.05. Such sample size does not allow to exclude chance findings in the associations of PCB exposure and B-NHL, consistent with the conclusion of the IARC Working Group (IARC, 2016). Additionally, our sample size may not have been sufficient to assess interactions by ethnic group as well as all secondary analyses. Second, as lipid concentrations were not measured, we used wet-weight concentrations of analytes measured rather than lipid-standardized concentrations. While the use of lipid-adjusted concentrations is controversial (Gaskins and Schisterman, 2009), estimates based on both wet-weight and lipid-adjusted concentrations of OC may be comparable (Ha et al., 2009; Lee et al., 2016). Further adjusting our estimates for body mass index, a predictor of serum concentrations of OC and PCBs (Pirard et al., 2017), did not attenuate the estimates for high-chlorinated PCBs. Third, the selection of cases and controls from the parent study was nonrandom and affected by serum availability. However, various characteristics such as age, smoking, and education in IJ and PA controls herein are comparable to those in the parent study, as is DLBCL predominance among PA cases (Kleinstern et al., 2017). Controls with a history of farming were added to better characterize this as source of OC exposure. Reassuringly, farming did not predict for higher concentrations of OC in controls. Further, although the addition of potentially exposed controls may have been expected to dilute the effect, excluding any study subjects with a history of farming slightly attenuated the associations. Fourth, the predominance of Ashkenazi Jews among IJ subjects requires caution when applying our findings to IJ of different ancestries. Lastly, 31 of 90 cases (34.4%) may have received treatment before sample draw. Both the administration of chemotherapy (Baris et al., 2000) and cancer progression (Porta et al., 2009) appear to decrease the body burden of OC, the latter possibly through faster metabolism of OC through weight loss (Wolff et al., 2005). However, restricting our analysis to pretreatment cases not change our findings.

5. Conclusions

We observed associations between high-chlorinated PCBs in serum and B-NHL. These associations, if further confirmed, support a modest contribution of high-chlorinated PCBs to NHL incidence. These findings warrant further investigation regarding sources of exposure and replication in larger populations, with possible stratification by occupational exposure, diet and infectious exposures.

Conflicts of interest

The authors have none to declare.

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Appendix A. Supplementary data

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