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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