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Prediagnostic Serum Concentrations of Organochlorine Pesticides and Non-Hodgkin Lymphoma: A Nested Case–Control Study in the Norwegian Janus Serum Bank Cohort

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Abstract

Background: Much of the marked increase in incidence of non-Hodgkin lymphoma (NHL) over the past few decades remains unexplained. Organochlorines, including organochlorine pesticides (OCPs), have been implicated as possible contributors to the increase, but the evidence is inconsistent.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Objectives: To investigate the relation between pre-diagnostic levels of OCPs and risk of NHL in a case-control study nested within the population-based Janus Serum Bank Cohort in Norway.

Methods: Prediagnostic concentrations of 11 OCPs or OCP metabolites were measured in baseline blood samples collected between 1972 and 1978 from 190 cases and 190 controls matched on sex, county, age at blood draw, and date of blood draw. We conducted conditional logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for each quartile of lipid-corrected OCP/metabolite relative to the lowest quartile.

Results: We observed non-significantly elevated ORs across quartiles of β-hexachlorocyclohexane compared to the lowest quartile (OR range: 1.40–1.82) although with no apparent monotonic exposure-response relationship. We also found an inverse association between risk of NHL and *o,p'*-DDT (OR for Q_4 vs. Q_1=0.44, 95% CI: 0.19, 1.01; p-trend=0.05). In analyses stratified by age at blood collection and duration of follow-up, several other analytes, primarily chlordane-related compounds, showed inverse associations among younger participants or those with longer follow-up time between blood draw and NHL diagnosis.

Conclusions: We found only limited evidence of positive association between selected OCPs and development of NHL.

Keywords

environmental pollutants; epidemiology; non-Hodgkin lymphoma; organochlorines; pesticides

1. INTRODUCTION

The incidence of non-Hodgkin lymphoma (NHL) rose steadily in North America and Europe in the latter half of the 20th century (Cartwright et al. 1999; Eltom et al. 2002; Sandin et al. 2006), although no further increase was observed after the mid-1990s (Adamson et al. 2007; Eltom et al. 2002; Sandin et al. 2006; Surveillance Research Program 2018). The secular trend, characterized by a rapid increase followed by a plateau of incidence in particular geographic regions, suggests that environmental factors may play a role in the etiology of NHL. Congenital and acquired immunosuppression constitutes the most well-established risk factor for NHL (Ekstrom-Smedby 2006; Skrabek et al. 2013). However, increased rates of HIV infection, use of immunosuppressive drug treatment, and changing diagnostic patterns cannot explain a substantial portion of the new cases (Hartge and Devesa 1992; Hartge et al. 1994; Palackdharry 1994). Several environmental pollutants, including organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), have been examined as potential contributing factors (Hardell and Eriksson 2003; Schottenfeld et al. 2006), with mixed results.

DDT and other OCPs, the first synthetic organic insecticides, were used extensively between the 1940s and 1960s to combat vector-borne diseases, such as malaria and typhus, and to control insects in agriculture (Beard 2006; Maroni et al. 2000). These chemicals are lipophilic, environmentally and biologically persistent, and capable of long-range transport (Iwata et al. 1994), which led to their widespread presence in the ecosystem and bioaccumulation in the biota worldwide (Jayaraj et al. 2016). Consequently, the general population was chronically exposed to OCPs, primarily via diet (Schecter et al.

2010) and intermittently through residential spraying to control mosquitoes, gypsy moths, and other pests (White et al. 2013). With increasing evidence of adverse toxicological and environmental effects, most OCPs were banned in the Western world by the 1980s, although application of DDT continues in several developing countries for control of malaria and leishmaniasis (van den Berg et al. 2017). Detectable levels of OCPs persist in the environment and much of the general population today (Patterson et al. 2009; Schecter et al. 2010).

Many OCPs are classified by the International Agency for Research on Cancer (IARC) (IARC 2019) as possible (Group 2B), probable (Group 2A), or known (Group 1) human carcinogens. Some OCPs have been associated with NHL, and researchers suggest the dysregulation of the immune system by OCPs' immunotoxic and endocrine-disrupting properties as a potential mechanism (Mokarizadeh et al. 2015). However, the epidemiologic evidence relating OCPs to NHL is inconsistent (Luo et al. 2016). Recent epidemiologic studies that measured OCPs in biospecimens found some associations between individual analytes and NHL risk (Bassig et al. 2019; Brauner et al. 2012; Hardell et al. 2009; Kelly et al. 2017; Quintana et al. 2004; Spinelli et al. 2007; Viel et al. 2011), but the specific analytes measured and associated with risk differ across studies. Possible explanations for the mixed results include differences in timing of collection or type of biological samples and residual confounding from correlated environmental contaminants, such as PCBs.

To date, only a few studies have measured OCPs in prediagnostic blood or adipose tissue and adjusted for other correlated organochlorine compounds (Cantor et al. 2003; Rothman et al. 1997). In the present nested case-control study, we examined NHL risk in relation to prediagnostic concentrations of organochlorines in serum samples collected in the 1970s, around the time of peak body burden of these chemicals, from participants in a population-based prospective cohort in Norway. This study complements a previous analysis of serum PCBs and risk of NHL among these study participants (Engel et al. 2007).

2. METHODS

2.1. Study Population

The Janus Serum Bank, established in 1973 with funding from the Norwegian Cancer Society, is a population-based biobank devoted to cancer research. Details on the Janus Serum Bank Cohort (N=318,628), including cohort enrollment, sample collection and quality, and participant characteristics have been described elsewhere (Langseth et al. 2017). In brief, blood specimens were collected for the Bank between 1972 and 2004 from enrolled participants. Almost 90% of participants were recruited from five rounds of cardiovascular health examinations in Oslo and selected counties in Norway in the 1970s-90s. Age at entry ranged from 19 to 50 years, with most enrolled between the ages of 30 and 49 years. Approximately 10% of cohort members were Red Cross blood donors enrolled from Oslo and surrounding areas, but who were not included in the present study. Sera from all participants were separated and have been stored at −25°C since collection. Cohort members provided a broad consent for their samples to be used for research purposes. The study was approved by the Regional committees for medical and health research ethics, Oslo, Norway

(REC no. 2010/3054) and by the institutional review boards of the other participating institutions.

We conducted a nested case-control study within the Janus Serum Bank Cohort among participants in the county health examinations who donated a blood sample during 1972–1978. Incident cases of NHL [*International Classification of Diseases, 8th Revision* (ICD-8) code 200 or 202] with no prior history of cancer (except possibly non-melanoma skin cancer) and with at least 1.0 mL of banked serum available for analysis were identified through linkage with the Cancer Registry of Norway using the national identification number and confirmed via a special review of pathology reports (Engel et al. 2007). We included all 194 cases who were diagnosed with NHL at least two years after cohort enrollment and through the end of 1998 (the most recent year available when the study data were collected). Using incidence density sampling and data from the Cancer Registry, one control was individually matched to each case by sex, county (Finnmark, Oslo, Sogn og Fjordane, or Oppland), age at examination (±1 year), and date of examination (±3 months) from among eligible cohort members with no NHL diagnosis at the time of the case ascertainment but otherwise according to identical criteria as the cases. Demographic data were obtained from the Cancer Registry of Norway and the Janus database. Self-reported smoking behaviors and anthropometric measurements, including height and weight that were used to construct BMI, were acquired at the original health examinations (Hjerkind et al. 2017).

2.2. Laboratory Assays

Concentrations of 11 OCPs or their metabolites [γ-hexachlorocyclohexane (γ-HCH), β-hexachlorocyclohexane (β-HCH), dieldrin, hexachlorobenzene (HCB), mirex, *p,p'*-dichlorodiphenyltrichloroethane (DDT), *o,p'*-DDT, *p,p'*-dichlorodiphenyldichloroethylene (DDE), heptachlor epoxide, oxychlordane, and *trans*-nonachlor] and lipid levels were measured at the National Center for Environmental Health of the U.S. Centers for Disease Control and Prevention in 0.6 mL of serum per participant, using published methods (Barr et al. 2003). Briefly, laboratory technicians first spiked sera with isotopically labeled internal standards and then purified them via automated accelerated solvent extraction and high-resolution gel permeation chromatography on a high-performance liquid chromatograph. Concentrated extracts were analyzed by gas chromatography/high-resolution mass spectrometry, and concentrations of OCP analytes were quantified from ^{13}C isotope dilution continuing calibration plots, which automatically corrected for extraction efficiency. Values below the instrumental limits of detection (LOD) were substituted with the instrumental LOD divided by $\sqrt{2}$ (Hornung and Reed 1990). Total lipid concentration was calculated for each subject using measurements of total cholesterol and triglycerides in an additional 0.1 mL serum (Phillips et al. 1989). Commercially available test kits (Roche Diagnostics Corp.; Indianapolis, IN) were used for quantitative determination of total cholesterol and triglycerides, and final measurements were made on a Hitachi 912 Chemistry Analyzer (Hitachi; Tokyo, Japan). Samples that belong to the same matched case-control set were analyzed together in the same batch. Masked quality control samples, including single samples from a large pool and pairs of replicate samples, were interspersed among study samples to assess interset and intraset variability. The serum samples from one

case and three controls were not successfully assayed, leaving 190 case-control pairs in the analytic sample with organochlorine measurements.

2.3. Statistical Analysis

All organochlorine measurements were corrected for total lipids (Phillips et al. 1989). Analyses were conducted for individual analytes, total DDT-related compounds (sum of *p,p'*-DDE, *p,p'*-DDT, and *o,p'*-DDT), and total chlordane-related compounds (sum of heptachlor epoxide, oxychlordane, and *trans*-nonachlor). Concentrations of groupings were calculated by converting the whole weight concentrations of all relevant analytes, including imputed values for samples whose concentrations were below the LOD, into moles and summing them. Lipid-corrected serum concentrations of analytes were categorized into quartiles, based on analyte-specific distributions among controls, with the lowest quartile as the referent group in the statistical analyses.

Conditional logistic regression stratified on matched pairs was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) of NHL. All regression analyses were additionally adjusted for BMI (tertiles), cigarette smoking status (never, former, current), and serum concentration of PCB congener 153 (quartiles), which were available for all participants included in our study. Selection of potential confounders was based on a minimally sufficient adjustment set identified in a directed acyclic graph (DAG) (Greenland et al. 1999), availability of data, and consistency with previously published literature on the topic (Supplemental Figure 1). We initially examined PCBs 118, 138, and 153 as potential covariates, based on their associations with NHL risk (Bertrand et al. 2010; Engel et al. 2007) and low to moderate correlations with the serum pesticide concentrations among our participants. Then, we employed a modified change-in-estimate approach recommended by Greenland et al. (2016) to select one or more PCBs to stay in the models. The method examined the tradeoff between bias and variance by calculating the mean squared error (MSE) when we dropped each PCB congener out of the models. Our final model that minimized MSE included PCB 153. Tests for exposure-response trend were conducted by modeling the median values of quartiles as a continuous measure (Mabikwa et al. 2017).

We conducted sub-analyses in which we stratified by time from blood draw to case diagnosis (median: <17 and ≥17 years) to explore whether risk of NHL differed by time from exposure ascertainment. Because some subtypes of NHL can have a relatively short latency, we also attempted to examine cases diagnosed within five and ten years of blood draw; however, too few cases accrued during these time periods (N=8 and N=34, respectively) to permit meaningful analysis. Additional stratified analyses were performed to investigate potential effect measure modification (EMM) of the OCP-NHL associations by age at blood draw (median: <44 and ≥44 years) and BMI (median: <24.2 kg/m^2 and ≥24.2 kg/m^2). Interaction models were constructed by inclusion of product terms of each OCP and the modifier, and likelihood ratio tests (LRTs) were performed on nested models to formally assess EMM on the multiplicative scale. We additionally conducted analyses restricted to men, but did not evaluate associations in women separately because of the small number of female cases (N=56). We also conducted sensitivity analyses by preserving the first three quartiles, but splitting the last quartile into two categories at the 90th percentile

(i.e. 25th, 50th, 75th, 90th percentile) of the control exposure distribution to see if patterns of association differed. Other sensitivity analyses that excluded cases and controls with extreme values for a given analyte were performed to examine the influence of potential outliers on the effect estimates. Because adiposity may both affect and be affected by body burden of organochlorines (Dirinck et al. 2011; Langer et al. 2014), analyses were run both with and without BMI as a covariate. As an alternative approach to adjust for serum lipids, we also included total lipids as a covariate in our models of lipid-corrected OCPs (O'Brien et al. 2016). To explore possible confounding among correlated OCPs, particularly in relation to the inverse associations observed for *o,p'*-DDT and chlordane-related compounds, we examined models that included pairs of these analytes. Lastly, because subtypes of NHL may have different etiologies, we assessed associations in a sub-analysis restricted to cases of B-cell lymphoma (N=130) and their matched controls. All statistical analyses were done using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). All tests were two-sided with α=0.05 significance level.

3. RESULTS

3.1. Study Population

The median age at enrollment was 44 years for both cases and controls. Among cases, the median age at diagnosis was 60.0 years (range, 31–73), and the median time from blood draw to NHL diagnosis was 16.6 years. BMI, cigarette smoking status, and, by design, the matching factors, were similar between cases and controls (Table 1), although slightly more cases were never-smokers and were in the highest tertile of BMI compared to controls.

3.2. Serum OCP Concentrations and Correlations

All OCP analytes had concentrations above the instrumental LOD in at least 77% of sera, with most having over 95% of samples above the LOD (Supplemental Table 1). Intraset and interset coefficients of variation (CVs) for each analyte among the quality control samples tended to be inversely related to the concentration of that analyte (Supplemental Table 2). Intraset CVs were below 10% for all analytes (median=6.0%) except for heptachlor epoxide (CV=23.0%). Interset CVs were relatively low (<20.0%) for about half of the analytes, but were above 30.0% for *o,p'*-DDT, heptachlor epoxide, γ-HCH, HCB, oxychlordane, and dieldrin (overall median CV=30.0%). The majority of OCPs were moderately correlated with each other (Supplemental Table 3). As expected, isomers and metabolites of DDT and chlordane, respectively, were more strongly correlated with each other (Spearman r=0.70–0.87 for DDT and 0.55–0.86 for chlordane).

3.3. Associations of OCP Analytes with NHL

Table 2 shows adjusted ORs of NHL for increasing quartiles of serum OCP concentration among all participants. ORs for NHL were elevated for the three upper quartiles of β-HCH relative to the first quartile (OR_2=1.40 [95% CI: 0.73, 2.67]; OR_3=1.82 [95% CI: 0.90, 3.69]; OR_4=1.40 [95% CI: 0.64, 3.04]), although risk estimates were not statistically significant and there was no evidence of a monotonic exposure-response relationship (p-trend=0.54). A significant inverse exposure-response trend was seen for *o,p'*-DDT (OR_2=0.76 [95% CI: 0.39, 1.51]; OR_3=0.67 [95% CI: 0.32, 1.38]; OR_4=0.44 [95% CI:

0.19, 1.01]; p-trend=0.05). A non-significantly reduced OR was observed for the highest quartile of heptachlor epoxide compared to the first quartile (OR=0.41, 95% CI: 0.15, 1.07), but there was no apparent exposure-response trend (p-trend=0.07).

3.4. Associations Stratified by Time to Diagnosis and Age at Blood Draw

When analyses were stratified by time from blood draw to diagnosis, we observed elevated ORs across quartiles of *p,p'*-DDT (OR range: 2.00–2.13) and *p,p'*-DDE (OR range: 1.77–2.95) in the earlier follow-up period; however, individual ORs were not statistically significant, nor was there evidence of an exposure-response relationship (p-trend=0.53 and 0.30, respectively) (Supplemental Table 4). In the late follow-up period, ORs for NHL remained elevated for the three quartiles of β-HCH compared to the referent group, but without a monotonic trend (OR range: 1.84–2.09). We also observed several inverse associations in this later follow-up period. Specifically, higher levels of *o,p'*-DDT were significantly associated with reduced odds of NHL (OR for Q_4 vs. Q_1=0.18, 95% CI: 0.05, 0.65), although the trend was not monotonic. An apparent exposure-response trend was seen for oxychlordane (OR_2=0.80, OR_3=0.42, OR_4=0.26; p-trend=0.02), and a similar but non-significant trend was observed for total chlordane (OR_2=0.89, OR_3=0.55, OR_4=0.32; p-trend=0.06). For *trans*-nonachlor, odds were substantially reduced in the highest quartile compared to the first quartile (OR for Q_4 vs. Q_1=0.21, 95% CI: 0.04, 1.03). ORs significantly differed across strata of time to diagnosis only for mirex (ρ=0.02), oxychlordane (ρ=0.03), chlordane (ρ=0.05), and *p,p'*-DDE (ρ=0.05).

When we stratified the analyses by age at blood draw, non-significantly elevated ORs were seen across quartiles of β-HCH (OR range: 2.21–2.86; p-trend=0.52) and *p,p'*-DDE (OR range: 2.19–3.94; p-trend=0.54) among those 44–50 years of age (Supplemental Table 5). Among those younger than 44 years at time of blood draw, a borderline inverse exposure-response was seen for dieldrin (OR_2=0.61, OR_3=0.38, OR_4=0.22; p-trend=0.07), and reduced odds of NHL were observed for the highest quartile of heptachlor epoxide (OR=0.08, 95% CI: 0.01, 0.49). In this younger age stratum, the two DDT isomers (*o,p'*-DDT, *p,p'*-DDT), total DDT-related compounds, and total chlordane-related compounds had significant tests of trend, but showed equivocal evidence of trends by quartiles. We observed heterogeneity in associations by age at blood draw for β-HCH (ρ=0.05), γ-HCH (ρ=0.02), heptachlor epoxide (ρ=0.02), *p,p'*-DDE (ρ=0.02), *p,p'*-DDT (ρ=0.01), and total DDT-related compounds (ρ=0.02). When analyses were restricted to men, results were similar to those among the full cohort (results not shown), although the trend for oxychlordane became somewhat stronger (OR_2=0.76, OR_3=0.64, OR_4=0.41; p-trend=0.06).

3.5. Sensitivity Analyses

Interpretation of associations remained similar when we additionally split the last quartile of each OCP at the 90th percentile, although the risk estimate for the highest category of heptachlor epoxide approached 1 (OR=0.87, 95% CI: 0.28, 2.64). Removal of extreme values in OCP measurements (one pair each for β-HCH, γ-HCH, *trans*-nonachlor, and mirex) produced minimal differences in the observed associations, and results are thus not shown. For total DDT and total chlordane, analyses treating them as sums of whole weights, rather than sums of moles, reached similar conclusions. Associations were similar when we

omitted BMI as a confounder, while analyses stratified by BMI produced substantially wider confidence intervals that impeded interpretation (results not shown). Adjusting for serum lipid as a covariate in the models produced similar associations. Results were also similar, albeit less precise, when we included serum concentrations of PCB 118 and 138 in the models. In models that included pairs of OCP analytes, we observed attenuated associations accompanied by wide confidence intervals that limited interpretation (results not shown). In analyses restricted to cases of B-cell lymphoma and their matched controls, risk estimates for β-HCH were no longer elevated, and heptachlor epoxide became inversely associated with NHL (p-trend=0.01) (Supplemental Table 6).

4. DISCUSSION

In this nested case-control study, we examined the associations between risk of NHL and prediagnostic serum levels of OCPs in a population-based cohort from Norway, using blood samples collected in the 1970s. We found limited evidence of increased NHL risk in relation to β-HCH, with non-significantly elevated ORs observed for all upper quartiles of β-HCH compared to the first quartile, but no evidence of a monotonic exposure-response trend. We also found evidence for a possible inverse exposure-response relationship between serum concentration of *o,p'*-DDT and risk of NHL (p-trend=0.05). In addition, we observed decreases in risk in relation to chlordane-related compounds among individuals who were younger at blood draw or were diagnosed later in the follow-up. These findings stand in contrast to those of an earlier study focused on PCBs in the same study population, which showed positive relationships between NHL risk and a number of PCB congeners (Engel et al. 2007).

The serum concentrations of OCPs in the current study, in particular *p,p'*-DDT and *p,p'*-DDE, are generally higher than those measured in most other European studies, which used more recently collected blood samples (Cocco et al. 2008; Hardell et al. 2009; Viel et al. 2011). This is not surprising because blood samples in our study were collected around the time most OCPs were banned in Norway (Johansen et al. 1994; Skaare et al. 1988) and other parts of Europe, and thus, are likely to reflect peak or near peak body burdens among Norwegians. While we observed a slight decrease in average serum concentrations of OCPs across years of blood draw, the reduction was small compared to the differences between quartiles.

The organochlorines investigated in our study were commonly applied in the United States and much of the world for several decades until the 1970s/1980s (ATSDR 2005, 2018; Breivik et al. 1999; Turusov et al. 2002), and have been studied in relation to other cancers (Khanjani et al. 2007; Lewis-Mikhael et al. 2015). Recent updates by IARC have classified lindane (γ-HCH) as carcinogenic (Group 1), with sufficient evidence in animals and humans of induction of liver tumors and NHL, respectively (Guyton et al. 2016). DDT and dieldrin are classified as probably carcinogenic to humans (Group 2A) (IARC 2019), based largely on induction of liver tumors in animal models and limited evidence of associations with liver and testicular cancers as well as NHL, in humans (IARC 2015). Other OCPs, including mirex, chlordane, heptachlor, technical lindane, and HCB, are classified as possibly carcinogenic (Group 2B) (IARC 2019). Possible mechanisms by which OCPs

might increase NHL risk include their apparent immunosuppressive effects (Mokarizadeh et al. 2015). Neoplastic transformation of T or B cells is often preceded by factors that dysregulate or suppress the immune system and allow Epstein-Barr virus (EBV)-driven B-cell proliferation and transformation (Ekstrom-Smedby 2006). The immunosuppressive effects of OCPs have been well documented in rodents (Barnett et al. 1985; Repetto and Baliga 1997; Spyker-Cranmer et al. 1982; Tryphonas et al. 2003), birds (Repetto and Baliga 1997), and human workers (Mokarizadeh et al. 2015). Additionally, many OCPs are endocrine disruptors (Langer 2010; Meeker et al. 2007; Mnif et al. 2011) and could contribute to risk of NHL by indirectly impairing the immune system (Chalubinski and Kowalski 2006; Mnif et al. 2011).

The risk of NHL was elevated for all categories of β-HCH compared to the lowest in the main and some subgroup analyses, although there was no apparent trend with increasing concentrations. Technical-grade HCH (60–70% α-HCH, 5–12% β-HCH, 10–15% γ-HCH, 6– 10% δ-HCH, and 3–4% ε-HCH) and later, technical-grade lindane (99.9% γ-HCH) were widely used as insecticides in agriculture (ATSDR 2005). Production of the commercial mixture ceased in the United States in 1976 (ATSDR 2005) and soon thereafter in Europe (Breivik et al. 1999). However, imported lindane is still permitted for use as a second-line treatment of head lice and scabies (Vijgen et al. 2011). IARC has classified lindane as carcinogenic (Group 1), based in part on its association with NHL (IARC 2015). Because it has a relatively short biological half-life and is frequently not detected in the general population, few studies have examined γ-HCH in relation to NHL risk, although a French study that did measure detectable levels found no association (Viel et al. 2011). β-HCH, which is more persistent and more widely detected in blood in the general population (ATSDR 2005), has been studied as a proxy indicator for historic exposure to technical-grade HCH. The analyte has been positively associated with NHL in several (Quintana et al. 2004; Spinelli et al. 2007; Viel et al. 2011) but not all (Brauner et al. 2012; Cantor et al. 2003; Cocco et al. 2008; De Roos et al. 2005) studies conducted in Western countries. Our results are consistent with a recent study that measured blood levels of OCPs in an Asian cohort study that found β-HCH was associated with increased risk of NHL in these non-Western populations (Bassig et al. 2019).

DDT, the first of the modern synthetic insecticides, was applied extensively worldwide to control vector-borne diseases, such as malaria and typhus, and for use on food crops. It was banned in the United States in 1972 (U.S. EPA 2017) and across most developed countries in the early 1970s (Park et al. 2014). While evidence for the association of NHL with DDT-related compounds is mixed, most biomarker-based studies have reported null findings for isomers of DDT (De Roos et al. 2005; Quintana et al. 2004) and its major metabolite, *p,p'*-DDE (Bassig et al. 2019; Bertrand et al. 2010; Brauner et al. 2012; Cocco et al. 2008; Colt et al. 2005; De Roos et al. 2005; Hardell et al. 2001; Hardell et al. 2009; Laden et al. 2010; Quintana et al. 2004; Viel et al. 2011). However, two studies with prediagnostic biospecimens found associations, including a positive association for *p,p'*-DDT (Brauner et al. 2012) and an inverse association for *p,p'*-DDE (Kelly et al. 2017). In contrast, self-reported DDT exposure has been associated with NHL in a handful of occupational studies of agricultural and industrial workers (Baris et al. 1998; Pahwa et al. 2012; Woods et al. 1987), including a recent meta-analysis (Schinasi and Leon 2014). The discrepancy in

findings may be attributable to generally higher occupational exposures compared to those among the general population and/or to potential recall bias from post-diagnostic interviews to assess exposure in most case-control studies. The present study, however, is the first to report an inverse association between NHL and *o,p'*-DDT. Fish consumption, a major component of the Norwegian diet and a primary source of OCP exposure (Alexander et al. 2006), has been associated with decreased risk of NHL (Caini et al. 2016; Skibola 2007), which might explain the suggestive inverse associations observed in the present study.

Previous studies are also inconsistent for chlordane-related analytes, some of which showed inverse associations in our subgroup analyses. As a commercial mixture, technical-grade chlordane consisted mainly of *trans*- and *cis*-chlordane, heptachlor, and *trans*-nonachlor (ATSDR 2018). It was used on food crops and to control termites before it was banned in the US in 1988 (ATSDR 2018). Most biomarker-based studies have observed no associations between NHL and oxychlordane (Bassig et al. 2019; Cantor et al. 2003; De Roos et al. 2005; Viel et al. 2011), heptachlor epoxide (Cantor et al. 2003; De Roos et al. 2005), *trans*-nonachlor (Bassig et al. 2019; Brauner et al. 2012; Cantor et al. 2003; De Roos et al. 2005; Quintana et al. 2004), or total chlordane (Brauner et al. 2012; Cantor et al. 2003), although positive associations were observed in some studies for oxychlordane (Brauner et al. 2012; Hardell et al. 2009; Quintana et al. 2004; Spinelli et al. 2007), heptachlor epoxide (Quintana et al. 2004), and *trans*-nonachlor (Hardell et al. 2009; Spinelli et al. 2007). Our study observed no clear evidence of risk associated with chlordane-related chemicals.

In our sub-analyses stratified by the median time from blood draw to NHL diagnosis or by age at blood draw, we observed several possible inverse associations among participants diagnosed in the later follow-up period or who were younger at blood draw. These associations were most apparent for *o,p'*-DDT and metabolites of chlordane, the latter being strongly correlated with one another. However, many of the risk estimates were not significantly different between strata. Previous studies that examined these factors found no differences in association by duration of follow-up (Brauner et al. 2012; Kelly et al. 2017; Laden et al. 2010) or by age (Kelly et al. 2017; Purdue et al. 2007; Spinelli et al. 2007). In addition, sub-analyses restricted to men produced similar results to those observed in the unstratified analyses, which is consistent with two previous studies (De Roos et al. 2005; Spinelli et al. 2007), although two other studies found stronger associations among men (Brauner et al. 2012; Kelly et al. 2017). The number of female cases in the cohort was too small for us to evaluate risks among this subgroup.

The putative causal relationship between body burden of OCPs and BMI, a proxy for adiposity (Pi-Sunyer 1998), is complicated by the complex interplay between patterns of exposure and changes in adiposity over time, both of which can affect OCP levels measured at a single point in time (Wolff et al. 2005). Many case-control and prospective cohort studies have noted obesity as a risk factor for NHL (Skibola 2007) or certain subtypes of NHL (Willett et al. 2008). If adiposity is on the causal pathway between OCP exposure and NHL development, adjusting for it would be inappropriate. We obtained similar results in models with and without BMI adjustment and chose to keep BMI in the model. Measurements of serum OCPs and adiposity across multiple time points in future studies would help clarify how to account for adiposity in the analysis of OCPs and NHL.

A major strength of our study is the use of prospectively collected biologic samples in a general population setting and follow-up of the cohort through the comprehensive Norwegian Cancer Registry. Blood samples collected prior to cancer diagnosis allow us to more clearly establish any temporal relationship between OCP exposure and incidence of NHL, as studies have shown that treatment of lymphoma may alter serum level of OCPs (Baris et al. 2000). Also, to minimize the likelihood that preclinical disease affected measured OCP levels, this study excluded cases diagnosed within two years after cohort enrollment. Because these chemicals have relatively long biological half-lives, their levels in blood, especially in specimens collected around the time of peak/near-peak use, are expected to provide a good estimate of long-term body burdens. Laboratory technicians were blinded to the case status of the sera, and samples in the same matched case-control set were analyzed in the same batch, both of which mitigated concerns about differential misclassification. A further strength of our study is the sensitivity of the laboratory methods, which allowed us to detect most pesticides in over 95% of samples. Available data on PCB congeners also allowed us to address potential confounding by these related organochlorine compounds.

This study also has a few limitations. Despite the relatively large sample size for a prospective study of NHL, we had limited power for stratified analyses. It should be noted that a related analysis among these study participants was able to detect significant exposure-response trends in relation to serum levels of certain PCB congeners (Engel et al. 2007). Further, histopathologic classification systems for NHL underwent substantial changes during the follow-up period (Armitage and Weisenburger 1998). We had sufficient histology information on most (83%) of our analytic sample to allow classification of cases into B-cell lymphoma, but analyses within finer groups of NHL (e.g. diffuse large B-cell lymphoma) were impeded by the lack of data and specimens necessary to standardize these classifications over time. Although etiology and risk factor profiles differ between certain NHL subtypes (Morton et al. 2014), studies to date have generally reported consistent relationships of OCPs and NHL across major subtypes (Bertrand et al. 2010; Cocco et al. 2008; Laden et al. 2010). When restricting to B-cell NHL, our risk estimates for β-HCH were substantially attenuated and chlordane became inversely associated with NHL, which may have resulted from the loss from our analyses of 34 cases with insufficient histology information to classify them as B-cell or T-cell. Another limitation of our study is the single serum sample available for exposure measurement, although these sera were collected around the time of peak/near-peak body burdens, and associations of other persistent organic pollutants with NHL have been observed using a single blood sample (Bertrand et al. 2010; De Roos et al. 2005; Engel et al. 2007). In addition, some degradation of serum lipids during storage is likely, as suggested by a stability study within the Janus Serum Bank (Gislefoss et al. 2015); however, it should be noted that a) the tight matching of cases and controls by date of blood draw is expected to render any resulting measurement error nondifferential by case status, although it may have attenuated risk estimates, and b) positive exposure-response trends were observed for certain PCB congeners measured together with these OCPs (Engel et al. 2007). Although we were able to adjust for correlated chemical exposures, we were not able to rule out the potential for residual confounding by other, unmeasured, lipophilic chemicals, such as dioxins and furans, which could have biased our risk estimates. However,

a previous study found little evidence of such confounding (De Roos 2005). We also lacked information on other potential confounders, such as reproductive history, physical activity, and diet (Grulich and Vajdic 2005; Skibola 2007), which have not been adjusted for in most other studies of OCPs and NHL. Lastly, the racial homogeneity of the Janus cohort increases internal study validity, but may limit this study's generalizability to other racial/ethnic groups.

In conclusion, we found limited evidence of adverse associations between prediagnostic serum levels of organochlorine pesticides and risk of NHL in this population-based nested case-control study in Norway. The few positive associations that we observed were not significant and showed no monotonic exposure-response relationships. However, we did observe a borderline significant inverse relationship for *o,p'*-DDT and possible inverse associations for some OCPs in subgroup analyses, but with generally little evidence of exposure-response trends. Additional research is needed to clarify the relationship between NHL, a disease with complex etiology, and OCPs, including consideration of histologic subtypes, as well as other racial/ethnic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CV	coefficient of variation
DAG	directed acyclic graph
HCB	hexachlorobenzene
HCH	hexachlorocyclohexane
IARC	International Agency for Research on Cancer
LOD	limit of detection
LRT	likelihood ratio test
NHL	non-Hodgkin lymphoma
OCP	organochlorine pesticide
PCB	polychlorinated biphenyl

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Highlights:

- Serum levels of 11 organochlorine pesticide analytes were measured in a cohort.
- Levels in this Norwegian cohort exceeded those observed in other European cohorts.
- These levels were examined in relation to incident non-Hodgkin lymphoma (NHL).
- Risks of NHL were elevated in upper quartiles of β-HCH, but with no apparent trend.
- A few inverse associations were found in subgroup analyses, possibly due to diet.

Table 1.

Selected characteristics of NHL cases and controls in the Janus cohort

Characteristic	Cases, n=190 n (%)	Controls, n=190 n (%)
Age in years at enrollment		
<30	4 (2.1)	4 (2.1)
30–40	40 (21.1)	36 (18.9)
40–45	59 (31.1)	63 (33.2)
>45	87 (45.8)	87 (45.8)
Median (min, max) years to diagnosis	16.6 (2.4, 25.3)	
Sex		
Male	134 (70.5)	134 (70.5)
Female	56 (29.5)	56 (29.5)
Cigarette use		
Current	84 (44.2)	91 (47.9)
Former	36 (19.0)	37 (19.5)
Never	70 (36.8)	62 (32.6)
BMI (tertiles)		
17.7–23.0	56 (29.5)	64 (33.7)
23.1–25.1	64 (33.7)	63 (33.2)
25.2–37.2	70 (36.8)	63 (33.2)
Year of enrollment/blood collection		
1972–1974	95 (50.0)	94 (49.5)
1975–1978	95 (50.0)	96 (50.5)

Note: NHL, non-Hodgkin lymphoma; BMI, body mass index

Table 2.

Adjusted ORs and 95% CIs for the risk of NHL in relation to quartiles of lipid-corrected serum concentrations of organochlorine pesticide analytes in the Janus cohort

Exposure, in quartiles (ng/g lipid)	Median (ng/g lipid)	Cases (n=190)	Controls (n=190)	OR[a] (95% CI)	p-Trend[b]
OC pesticide analyte					
Chlordane [c]					
Q1 (8.2–31.0)	23.5	39	47		0.25
Q2 (31.1–44.9)	37.5	60	48	1.56 (0.81, 3.01)	
Q3 (45.3–60.5)	51.5	45	47	1.09 (0.53, 2.22)	
Q4 (60.6–202.6)	75.0	46	48	0.72 (0.32, 1.62)	
Oxychlordane					
Q1 (0.3–10.5)	8.0	49	47		0.21
Q2 (10.5–14.5)	12.6	47	46	0.99 (0.54, 1.81)	
Q3 (14.5–19.2)	16.7	49	47	0.92 (0.47, 1.79)	
Q4 (19.6–71.6)	24.9	44	46	0.63 (0.30, 1.32)	
trans-Nonachlor					
Q1 (3.8–14.7)	11.9	40	48		0.32
Q2 (14.7–20.7)	17.5	51	48	1.29 (0.66, 2.52)	
Q3 (20.7–29.6)	24.3	57	47	1.39 (0.70, 2.79)	
Q4 (29.6–95.4)	37.3	42	47	0.71 (0.29, 1.72)	
Heptachlor epoxide					
Q1 (0.2–8.1)	6.2	41	39		0.07
Q2 (8.2–10.8)	9.6	42	38	0.95 (0.46, 1.99)	
Q3 (10.8–14.6)	12.3	49	39	1.03 (0.48, 2.19)	
Q4 (14.6–50.0)	17.6	30	38	0.41 (0.15, 1.07)	
DDT [c]					
Q1 (92.2–3014.4)	2320.1	46	47		0.30
Q2 (3085.8–4620.8)	3954.6	51	48	0.97 (0.52, 1.83)	
Q3 (4693.5–6732.1)	5570.2	47	48	0.79 (0.38, 1.65)	
Q4 (6742.7–28123.3)	8567.9	46	47	0.67 (0.29, 1.58)	
p,p´-DDT					
Q1 (7.9–134.6)	101.4	44	47		0.56
Q2 (135.6–230.8)	178.0	48	48	1.06 (0.56, 2.02)	
Q3 (230.8–347.0)	276.7	52	48	1.06 (0.51, 2.19)	
Q4 (350.9–1116.5)	450.9	46	47	0.82 (0.35, 1.92)	
p,p´-DDE					
Q1 (75.4–2518.2)	1937.1	39	47		0.89
Q2 (2565.7–3981.9)	3346.9	50	48	1.25 (0.65, 2.41)	
Q3 (4038.1–5757.2)	4715.5	52	48	1.18 (0.60, 2.31)	
Q4 (5875.1–24352.1)	7230.1	49	47	1.13 (0.52, 2.47)	
o,p´-DDT					

Exposure, in quartiles (ng/g lipid)	Median (ng/g lipid)	Cases (n=190)	Controls (n=190)	OR[a] (95% CI)	p-Trend[b]
Q1 (0.3–10.9)	7.8	52	47		0.05
Q2 (10.9–20.0)	14.5	49	48	0.76 (0.39, 1.51)	
Q3 (20.0–33.3)	25.6	51	48	0.67 (0.32, 1.38)	
Q4 (33.4–189.7)	48.2	37	47	0.44 (0.19, 1.01)	
Hexachlorobenzene					
Q1 (68.9–350.0)	243.7	46	47		0.63
Q2 (350.1–510.5)	422.2	50	48	0.96 (0.47, 1.99)	
Q3 (511.3–758.8)	622.9	44	48	0.77 (0.32, 1.86)	
Q4 (772.8–4688.7)	937.0	50	47	0.79 (0.29, 2.17)	
γ-Hexachlorocyclohexane					
Q1 (0.1–4.0)	3.1	53	46		0.97
Q2 (4.1–5.9)	4.9	48	47	0.80 (0.43, 1.50)	
Q3 (6.0–7.8)	6.7	33	47	0.57 (0.28, 1.14)	
Q4 (7.8–45.3)	9.4	55	47	1.03 (0.50, 2.09)	
β-Hexachlorocyclohexane					
Q1 (48.5–98.7)	83.0	35	48		0.54
Q2 (101.2–137.5)	118.3	49	48	1.40 (0.73, 2.67)	
Q3 (137.6–181.5)	156.2	57	47	1.82 (0.90, 3.69)	
Q4 (181.9–1598.9)	222.3	49	47	1.40 (0.64, 3.04)	
Dieldrin					
Q1 (0.1–18.0)	4.6	51	47		0.68
Q2 (19.3–40.9)	29.3	45	46	0.81 (0.41, 1.57)	
Q3 (41.2–63.3)	50.2	36	47	0.55 (0.25, 1.24)	
Q4 (64.1–248.4)	83.2	52	46	0.78 (0.33, 1.87)	
Mirex					
Q1 (0.02–0.8)	0.7	40	47		0.84
Q2 (0.8–1.2)	1.0	46	46	1.06 (0.57, 1.94)	
Q3 (1.3–2.0)	1.6	52	45	1.30 (0.68, 2.47)	
Q4 (2.0–7.8)	3.0	50	46	1.12 (0.55, 2.27)	

Note: NHL, non-Hodgkin lymphoma; OC, organochlorine; DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethylene; OR, odds ratio; 95% CI, 95% confidence interval

a. Adjusted for BMI (tertiles), smoking status (current, former, and never), PCB153 (quartiles), and the matching factors of sex, county, age at examination, and date of examination

b. Trend across the median values of quartiles

c. Concentrations based on nanomoles, rather than nanograms, per gram lipid