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A nested case-control study of polychlorinated biphenyls, organochlorine pesticides, and thyroid cancer in the Janus Serum Bank cohort

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Abstract

Background—Polychlorinated biphenyls (PCBs) and organochlorine pesticides have been associated with altered thyroid hormone levels in humans, but their relationship with thyroid cancer is unknown.

Methods—We conducted a nested case-control study of thyroid cancer in the Norwegian Janus Serum Bank cohort using pre-diagnostic blood samples from 1972-1985. Incident thyroid cancer (n=108) was ascertained through 2008. Controls were matched 2:1 by age, date of blood draw, gender, and county. We used gas chromatography/mass spectrometry to quantify 36 PCB congeners and metabolites of pesticides DDT, chlordane, hexachlorocyclohexane, and hexachlorobenzene. PCBs and pesticide metabolites were evaluated individually and summed by

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Human Subjects Protections:

The study was reviewed by the National Cancer Institute's Office of Human Subjects Research Protections, and it was determined at the National Center for Environmental Health that the agency was not engaged in human subjects' research. The study was approved by the Norwegian regional committee for medical and health research ethics (REC no. 2010/692).

degree of chlorination and parent compound, respectively. Odds ratios (OR) and 95% confidence intervals (CI) were computed using conditional logistic regression per specified increase in lipid-adjusted concentration. We additionally stratified analyses by birth cohort (1923-1932-1933-1942-1943-1957).

Results—Increasing concentration of DDT metabolites (ORper 1000ng/g=0.80, 95%CI=0.66-0.98) was inversely associated with thyroid cancer. Associations for PCBs were null or in inverse direction. We observed interactions for total PCBs, moderately-chlorinated PCBs, and chlordane metabolites with birth cohort ($p \leq 0.04$). Among participants born 1943-1957, total PCBs ($OR_{per\ 100ng/g}$=1.25, 95%CI=1.00-1.56), moderately-chlorinated PCBs ($OR_{per\ 100ng/g}$=1.31, 95%CI=1.01-1.70), and chlordane metabolites (ORper 10ng/g=1.78, 95%CI=1.09-2.93) were positively associated with thyroid cancer. For individuals born before 1943, associations were generally null or in the inverse direction.

Conclusions—Emissions of PCBs and OC pesticides varied over time. Different risk patterns by birth cohort suggest the potential importance of timing of exposure in thyroid cancer risk. Further evaluation of these associations is warranted.

Keywords

Polychlorinated biphenyls; Organochlorines; Chlordane; DDT; Thyroid Cancer

1. INTRODUCTION

Thyroid cancer is one of the most commonly diagnosed cancers among women in the United States (US), and incidence rates among both men and women have increased 211% since 1975 (Lim et al., 2017; Siegel et al., 2017). These patterns are not unique to the US; studies show that thyroid cancer rates have increased in most developed and developing countries worldwide (Engholm et al., 2010; Kilfoy et al., 2009). While increased detection of small, non-aggressive tumors may in part explain this upward trend, a growing body of literature has demonstrated that incidence rates for larger and advanced-stage thyroid cancers are also rising (Enewold et al., 2009; Lim et al., 2017).

Organochlorine (OC) compounds are man-made organic substances that contain one or more chlorine atoms, and include polychlorinated biphenyls (PCBs) and OC pesticides (Pelletier et al., 2003). Due to their chemical structure, OCs are both stable and lipophilic (Kutz et al., 1991); they have long half-lives and may persist in the environment and adipose tissue for many years (Pelletier et al., 2003). PCBs were manufactured beginning in 1929, and production peaked in the 1950s-1970s (IARC, 2016). They were widely used in industry as dielectric fluids in capacitors and transformers, and commercially as elastic sealants, flame-retardant coatings, and in other household items such as paints, finishes, and light fixtures (IARC, 2016; DellaValle et al., 2013). PCB use was banned in most countries by the 1980s due to concerns about toxicity and environmental persistence (EPA, 1979; Füll, 2001; Kutz et al., 1991). After World War II, OC pesticides were used globally for pest control until the 1960s-1970s, when most were banned primarily due to environmental concerns (Kutz et al., 1991). Dichlorodiphenyltrichloroethane (DDT) is a well-known OC insecticide that was used widely in agriculture, and still has limited use for the eradication of vector-borne

diseases such as malaria (Loomis et al., 2015). Chlordane was used residentially on lawns and shrubbery, in agriculture for common crops such as corn and potatoes, and by professional applicators for eradication of termites (IARC, 2001). Occupational exposures to PCBs (e.g. capacitor manufacturing, construction or demolition) and OC pesticides (e.g. agriculture) were historically a source of exposure in certain industries and may still play a small role (DellaValle et al., 2015; Kutz et al., 1991). However, diet is the most common route of exposure for the general population, particularly through consumption of contaminated fatty foods such as fish, meat, and dairy products (Pelletier et al., 2003).

Many PCBs and OC pesticides have demonstrated thyroid hormone-disrupting effects in laboratory and cross-sectional molecular epidemiologic studies (Brouwer et al., 1999; Brucker-Davis, 1998; Langer, 2010). Studies in laboratory animals have found that exposure to PCB mixtures and specific OC pesticides (i.e. chlordane, hexachlorobenzene [HCB]) increased incidence of thyroid tumors (IARC, 2001; IARC, 2016). Few epidemiologic studies have assessed associations between environmental exposure to OCs and thyroid cancer, with mixed findings. Spanish residents living near a factory producing chlorinated organic compounds had excess thyroid cancer incidence compared to the rest of the province (Grimalt et al., 1994). The authors attributed the association to the high levels of HCB in the sera of residents living near the factory, which was being emitted as a by-product in the production of other OCs. In Slovakia, thyroid cancer incidence rates were lower among women, but not men, residing near a PCB production facility compared to a similar nearby population with substantially lower levels of environmental contamination (Pavuk et al., 2004). A small cohort study of fishermen in upstate New York in an area with known PCB contamination used extensive information on the amount and type of consumption of local fish to evaluate PCB exposure and thyroid cancer risk (Haslam et al., 2016). The authors found an inverse association with thyroid cancer risk, though they attributed this association not to PCBs but to the high omega-3 fatty acid content of fish, high consumption of which has been associated with reduced risk of some cancers (Tavani et al., 2003). Some evidence has emerged from occupational settings as well, such as excess thyroid cancer mortality among capacitor manufacturing workers with occupational exposure to PCBs (Mallin et al., 2004). However, the applicability of these occupational findings to exposures in the general population, where route of exposure, PCB congener mixture, and dose may differ, is unclear.

These prior epidemiologic studies of OCs and thyroid cancer used indirect measures of exposure and had limited power due to small numbers of cases. To our knowledge, no published study has examined pre-diagnostic serum concentrations of PCBs or OC pesticide metabolites and thyroid cancer. To address the hypothesis that these chemicals may influence thyroid cancer risk, we conducted a nested case-control study of thyroid cancer within the Janus Serum Bank Cohort in Norway.

2. MATERIALS AND METHODS

2.1 Study population

The Janus Serum Bank Cohort was established in 1973 with funding from the Norwegian Cancer Society for the purposes of conducting cancer research. The cohort recruitment, specimen collection, and participant characteristics has been described (Langseth et al.,

2017). Briefly, blood specimens from the Janus Cohort (n=318,628 individuals) came from two main sources: participants in the Norwegian Regional Health Studies in selected counties in Norway (~90%), and Red Cross blood donors (~10%) from Oslo and surrounding areas. Blood specimens were collected from 1972-2004 with age at blood draw ranging from 18-65 (mean=41). Janus participants gave broad consent for their blood specimens to be used for research activities (Langseth et al., 2017).

Within the Janus Serum Bank Cohort, we conducted a nested case-control study of thyroid cancer with individual matching on age at blood draw (within one year), gender, blood draw date (within three months), and region (Oslo, Oppland, Sogn og Fjordane, Finnmark). We selected cohort participants with blood draws from 1972-1985, no prior cancer diagnosis (except nonmelanoma skin cancer), and at least 0.80 mL of serum available. We included incident first primary thyroid cancer cases ascertained through 2008, who were diagnosed at least one year after their blood draw. Most tumors were the papillary subtype (International Classification of Disease for Oncology histology codes 8050, 8260, 8340-8341, 8343-8344, 8350), all other histologies were grouped as other (Egevad et al., 2007).

2.2 Laboratory Analysis

Metabolites of 37 PCB International Union of Pure and Applied Chemistry congeners (28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 114, 118, 123, 128, 138/158, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196/203, 199, 206, and 209) and five OC pesticides including DDT (*p,p′*-dichlorodiphenyldichloroethylene [*p,p′*-DDE], *p,p′*-DDT, *o,p′*-DDT), chlordane (oxychlordane, trans-nonachlor), lindane (*γ*-hexachlorocyclohexane [*γ*-HCCH], isomer and byproduct of lindane production *β*-HCCH), mirex, and HCB were measured in serum at the Centers for Disease Control and Prevention, National Center for Environmental Health, using methods that have been described (Sjodin et al., 2004). Briefly, sample processing involved automatic fortification of sera samples using internal standards, and addition of formic acid and water for denaturation and dilution of the samples using a Gilson 2150 liquid handler (Gilson Inc., Middleton, WI). Samples were then extracted by solid phase extraction (SPE) using a Rapid Trace modular SPE system (Caliper Life Sciences; Hopkinton, MA). Removal of co-extracted lipids was performed on a silica/sulfuric acid column using Rapid Trace equipment for automation. Final analytic determination of the target analytes was performed using gas chromatography isotope dilution high resolution mass spectrometry employing a MAT95XP instrument (ThermoFinnigan MAT; Bremen, Germany) (Sjodin et al., 2004). Serum lipid concentration was determined using commercially available test kits (Roche Diagnostics Corp.; Indianapolis, IN) for quantitative determination of total triglycerides and total cholesterol, with final determinations made on a Hitachi 912 Chemistry Analyzer (Hitachi; Tokyo, Japan).

Masked quality-control samples, including seven pairs of replicate samples and 31 samples from a large pool (1-2 per batch), were interspersed among study samples to assess intra-batch and inter-batch variability. Case-control matched pairs were placed randomly within the same batch. Intra-batch coefficients of variation (CV) were <10% for 79% of the analytes measured (median=7.1%, range=3.8-49.5%). We noted CVs >20% indicating lower

laboratory reproducibility for four analytes: PCB 87 (38.6%), 114 (36.0%), and 189 (49.5%), and oxychlordane (37.2%). To assess possible inter-batch effects, we ran the same blinded pooled quality control (QC pool) sample across each of the 19 batches (31 QC pool samples total) and compared the mean concentrations. No batch effects were observed; reported results are based on all batches.

Analytes with >20% of values below the limit of detection (LD) were excluded from the analysis (PCB 123, mirex, γ-HCCH). Ranges for lipid-adjusted LDs are provided in the supplementary material (Table S1). Of the remaining analytes, 23 of 36 PCB congeners and 4 of 9 OC pesticide metabolites had values below the LD, ranging from <1% (PCB 74) to 19% (*o,p*'-DDT). We imputed lipid-adjusted values (analyte divided by total lipid concentration) below the LD five times using a parametric model-based estimation procedure based on a lognormal distribution (Lubin et al., 2004). Age at blood draw, gender, case-control status, and correlated analytes were included in the model as covariates.

PCB congeners were analyzed individually and summed across groups which characterized them by their chemical properties and hypothesized biological effects *in vivo* (low chlorinated: PCB 28, 44, 49, 52, 66, 74, moderately chlorinated: PCB 87, 99, 101, 105, 110, 114, 118, 123, 128, 138/158, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, high chlorinated: PCB 194, 195, 196/203, 199, 206, 209, thyroid-like: PCB 28, 52, 74, 99, 101, 105, 114, 118, dioxin-like: PCB 105, 114, 118, 123, 156, 157, 167, 189, Wolff 1A: 44, 49, 52, Wolff 1B: 101, 177, 187, Wolff 2A: 66, 74, 105, 118, 156, 167, Wolff 2B: 128, 138/158, 170, Wolff 3: 99, 153, 180, 196/203) (IARC, 2016; Wolff et al., 1997). Metabolites of DDT (*p,p′*-DDE, *o,p′*-DDT, and *p,p′*-DDT), and chlordane (oxychlordane and *trans*-nonachlor) were analyzed individually and as the sum for each pesticide.

2.3 Statistical analysis

Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between each lipid-adjusted analyte on thyroid cancer. Reported ORs reflect associations for a 1, 10, 100, or 1000-unit change in analyte concentration (ng/g lipid), based on the range of reported values: <50, 50-499, 500-4999, ≥5000, respectively. Individuals with non-reportable values (ranging from 0 to <5% of participants for all analytes) due to interferences and/or the analytical runs falling outside of characterization limits were excluded from that analysis. We additionally evaluated PCB and OC exposures as tertiles, with the lowest tertile of exposure as the referent category. Tests for trend modeled the median of each tertile as a continuous variable. As a sensitivity analysis, we conducted unconditional logistic regression models adjusted for the matching factors.

Additional covariates from the Norwegian Regional Health Studies were available for about 75% of our study population (Hjerkind et al., 2017). We considered body mass index (BMI; <25, ≥25) and smoking status at interview (never, former, current) as potential confounders. Missing values were imputed five times using a parametric model-based approach for BMI and stratified random sampling from the empirical frequency distribution derived from those with non-missing data for smoking status (Heltshe et al., 2012; Lubin et al., 2004). We performed sensitivity analyses restricting to papillary thyroid cancer, the most common

tumor subtype (n=92 cases), and also including only case/control triads where the case was diagnosed more than five years after blood draw (n=102 cases). We stratified analyses by gender, county of residence at blood draw, and birth cohort (1923-1932-1933-1942-1943-1957). When year of birth of matched cases and controls differed, birth cohort was assigned based on the case's year of birth (if different) as to not break the match. For stratified analyses, p-values for multiplicative interaction were calculated (e.g. PCB 153 × gender).

Statistical analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC). All tests were two-sided with α=0.05.

3. RESULTS

Our study population consisted of 108 thyroid cancer cases and 216 matched controls (Table 1). Over 85% of thyroid cancers in our study were papillary thyroid cancers (n=92); most of the rest were follicular thyroid cancers. Most thyroid cancer cases were diagnosed between the ages of 51-65, with a median age of 59 years. The median age at blood draw was 41 years, and participants were followed for a median of 21 years. Cases and controls did not differ by the matching characteristics including age at enrollment, blood draw year, sex, and county of residence. Cases and controls also did not differ in BMI or smoking status, although more cases were nonsmokers and fewer were current smokers. Cases and controls had similar total cholesterol levels; however, cases had higher levels of total triglycerides compared to controls (p=0.08, chi-square test for homogeneity).

Spearman correlations were high among measured OC analytes (Supplemental Material, Figure S1). Generally, PCBs were highly correlated with other PCB congeners with similar levels of chlorination (low: 0.33-0.95, moderate: 0.25-0.97, high: 0.69-0.95). Low and moderately chlorinated PCBs were moderately correlated (ρ=51), while moderately and highly chlorinated PCBs were highly correlated (ρ=0.84); low and highly chlorinated PCBs are relatively uncorrelated (ρ=0.29). Wolff groups 1B to 3 were highly correlated (0.81-0.98), with groups 2B and 3 almost perfected correlated (ρ=0.98). OC pesticide metabolites of the same parent chemical were highly correlated, including chlordane metabolites oxychlordane and *trans*-nonachlor (ρ=0.84) and DDT metabolites *p,p′*-DDE and *o,p′*-DDT (ρ=0.85).

In Table 2, we present concentration distribution and conditional logistic regression model results for analytes with median concentrations of at least 15 ng/g lipid (16 of 36 PCB congeners and 6 of 7 OC insecticide metabolites). Results for all PCBs and OC insecticides are included in the Supplemental Material (Table S1). In general, median serum concentrations for PCBs and OC insecticides were higher among controls compared to thyroid cancer cases. PCB 114 was inversely associated with thyroid cancer (Table S1; $OR_{per1ng/g}$=0.78, 95% CI 0.62-0.97), although the median concentrations were low in cases and controls (2.1 and 2.4 ng/g lipid, respectively). Higher sum of three DDT metabolites ($OR_{per1000ng/g}$=0.80, 95% CI=0.66-0.98) and *p,p′*-DDE ($OR_{per1000ng/g}$=0.79, 95% CI=0.64-0.97) was inversely associated with thyroid cancer. There were no significant associations for any other PCBs or OC pesticide metabolites. Results for unconditional

logistic regression models adjusted for matching factors were very similar in magnitude and direction (not shown).

We observed statistically significant interactions for the sum of PCBs, moderately chlorinated PCBs, and chlordane metabolites with birth cohort (Table 3). Among study participants born in 1943 and later, higher total ($OR_{per100ng/g}$=1.25, 95% CI=1.00-1.56) and moderately-chlorinated PCBs ($OR_{per100ng/g}$=1.31, 95% CI=1.01-1.71) were positively associated with thyroid cancer; significant interactions and positive associations with thyroid cancer were also observed for individual congeners including PCBs 138/158, 146, 153, and 183. We observed positive associations with Wolff groups 2B and 3 and thyroid cancer in the youngest birth cohort that appear to be driven by high-concentration PCBs 138 and 153, respectively. Higher sum of chlordane metabolites ($OR_{per10ng/g}$=1.78 95% CI=1.09-2.93), and specifically *trans*-nonachlor ($OR_{per10ng/g}$=2.43 95% CI=1.11-5.34), was associated with thyroid cancer. Among participants born before 1943, *trans*-nonachlor was inversely associated with thyroid cancer among those born in 1923-32. Higher sum of DDT metabolites was inversely associated with thyroid cancer among all birth cohorts, with the strongest association for participants born in 1923-1932 ($OR_{per1000ng/g}$=0.69 95% CI=0.49-0.98). Serum OC concentrations tended to be higher among the oldest cohort, and lower among the youngest cohort (Supplemental Material, Table S2). We used different birth year cut-offs (e.g. 1923-1920 [1920s], 1930-1939 [1930s], 1940-1957 [1940s/50s]) to evaluate the robustness of birth cohort groups, and found that while the point estimates varied slightly, the general pattern of significantly increased odds ratios among individuals born after 1940 was apparent.

No substantial associations were observed for thyroid-like or dioxin-like PCBs overall (Table 2) or by birth cohort (Table 3). Adjustment for BMI and smoking status resulted in only minor changes to the ORs (Supplementary Material, Table S3). Results stratified by gender and county of residence at blood draw were similar to overall findings (not shown). When we restricted our analyses to papillary thyroid cancers and study participants with at least five years of follow-up, the overall and stratified results were similar (not shown). Models evaluating tertiles of exposure, with the lowest tertile as the referent category, demonstrated similar results compared to continuous exposures (Supplemental Material, Table S4).

4. DISCUSSION

In this first published study to examine pre-diagnostic serum concentrations of PCBs and OC pesticides and thyroid cancer, we found an inverse association for *p,p′*-DDE, the DDT metabolite found in serum at the highest concentrations. We also observed interactions with birth cohort. Among individuals in the youngest birth cohort (1943-1957), we observed positive associations with increasing concentrations of total PCBs, moderately-chlorinated PCBs, and metabolites of the insecticide chlordane, but generally null associations for earlier birth cohorts PCBs are classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC) based on animal evidence, consistent epidemiologic evidence for associations with melanoma, and less consistent findings with non-Hodgkin lymphoma (NHL) and breast cancer (IARC, 2016). Few epidemiologic studies have

examined thyroid cancer and occupational or environmental exposure to PCBs, and none have examined serum concentrations of PCBs. We examined 36 PCB congeners individually and summed by degree of chlorination, which along with chlorine positions has been shown to influence the chemical and physical properties of these compounds. Overall, PCBs were not associated with thyroid cancer in our study, with the exception of PCB 114 which was present at low concentrations and was inversely associated with thyroid cancer. The interpretation of a reduced risk for a single congener among many correlated PCBs with much higher concentrations is not clear. Concentrations of several other PCB congeners were weakly inversely associated with risk (e.g. PCB 99, PCB 199). A small study in upstate New York estimated total PCB and omega-3 fatty acid exposure based on amount and type of fish consumed, and observed protective effects for both (Haslam et al., 2016). They attributed their inverse findings for PCBs to omega-3 fatty acids, the effects of which were difficult to separate from PCBs based on the exposure assessment method. However, a prior study in the Janus Serum Bank cohort found that while serum concentrations of long-chain fatty acids were protective against thyroid cancer risk, there was no association with the ratio of eicosapentaenoic acid to arachidonic acid, which is used to indicate consumption of fats from fish (Berg et al., 1994). Moreover, a registry linkage study in Norway found that women married to fishery workers had elevated incidence of thyroid cancer, and authors suggested seafood consumption as a potential etiologic risk factor (Frich et al., 1997). Fish is the major dietary source of PCBs in Norway, with oily and semi-oily fish and fish liver/roe accounting for more than half of dietary exposure (Kvalem et al., 2009). Evidence that fish consumption is protective against thyroid cancer and may confound the relationship with PCBs is still very limited, and requires further study.

Several OC pesticides have been classified by IARC according to their carcinogenicity, including lindane (γ-HCCH, Group 1, carcinogenic to humans), DDT (2A, probably carcinogenic to humans), chlordane (2B, possibly carcinogenic to humans), and HCB (2B) (IARC, 2017). None of these classifications were based on strong evidence of thyroid tumors in epidemiologic or laboratory studies (IARC, 2001; Loomis et al., 2015). In our study, we observed an inverse association with DDT metabolites, which did not differ significantly by birth cohort. Serum concentrations in our study population of the major DDT metabolite *p,p´*-DDE were high, with a median of approximately 1800 ng/g lipid, orders of magnitude higher than other analytes measured. There is some evidence to suggest that DDT metabolites interfere with thyroid hormone transport and metabolism (Brucker-Davis, 1998); however, the direct impact on thyroid cancer risk is unknown.

Among participants in the youngest birth cohort (1943-1957), we observed positive associations with thyroid cancer for total PCBs and the sum of the moderately chlorinated PCBs including 138/158 and 153. These PCBs are among the most commonly measured in epidemiologic studies due to their presence at relatively high concentrations in serum (IARC, 2016). There is some evidence for the carcinogenicity for PCB 153 *in vivo* based on increased incidence of liver tumors in rats (NTP, 2006). The evidence for carcinogenicity of PCB 138 in laboratory animals is inadequate based on few, low-quality studies (IARC, 2016). Epidemiologic biomarker studies examining other hormonally-related cancer sites such as breast, prostate, and testicular germ cell tumors have observed inconsistent or null associations for these congeners, though they have been associated with increased risk of

NHL in the general population including a prior analysis in the Janus Serum Bank Cohort (IARC, 2016; De Roos et al., 2005; Engel et al., 2007). In evaluating PCB congeners grouped by their chemical and biological properties, we found that among the youngest birth cohort, the Wolff PCB groups 2B and 3 (ρ=0.98) were associated with increased thyroid cancer risk. Associations with thyroid-like and dioxin-like PCBs were elevated in the youngest birth cohort but not significant. The association with the Wolff groups may be driven by high-concentration PCBs present in these groupings (e.g. PCB 153 in Wolff group 3) and/or potential effects on thyroid hormones based on their structural, biological, and pharmacokinetic properties (Moysich et al., 1999; Wolff et al., 1997). Literature suggests that PCBs may affect thyroid function via receptor-mediated mechanisms or changes in thyroid hormone metabolism (Brouwer et al., 1999).

We additionally noted positive associations for chlordane metabolites among individuals in the youngest birth cohort. Associations between chlordane and thyroid cancer have not been previously reported in the literature, though many epidemiologic studies have examined occupational and environmental chlordane exposures and associations with other cancer sites (IARC, 2001). The most consistent finding is for NHL, which has been associated with both self-reported chlordane exposure (Colt et al., 2006), measured levels in the home (Colt et al., 2005), and serum measures of chlordane metabolites (Luo et al., 2016). In rats, chlordane exposure has been consistently associated with thyroid effects, including increased incidence of thyroid tumors and decreases in thyroxine concentration (IARC, 2001).

The interactions between birth cohort and exposures to PCBs and chlordane suggests that age at exposure may be an important determinant of risk. Models of PCB serum concentrations over the lifetime demonstrate that birth cohort is an important determinant of age at first and peak exposure (Quinn et al., 2011). PCB and OC pesticide production increased dramatically in the mid-1940s and peaked about 20 years later (IARC, 2016; Kutz et al., 1991). Exposure models indicate that individuals born in the 1940s-1950s were most likely to have been exposed to OCs during childhood and adolescence; whereas earlier birth cohorts would have been exposed only at older ages. A pattern of increased risk of thyroid cancer and thyroid nodules with exposure during childhood has been demonstrated for radiation, an established thyroid carcinogen, indicating that the thyroid gland is most susceptible to the carcinogenic effects of radiation during childhood (Cahoon et al., 2017; Cardis et al., 2005; Tronko et al., 2017). Moreover, a study examining serum DDT metabolites in young adult women and pre-menopausal breast cancer noted associations only among women exposed prior to age 14, (Cohn et al., 2007), indicating that hormone-disrupting effects of OCs may influence carcinogenesis only when they are experienced during specific critical developmental windows. Cohn et al. similarly used birth year as a proxy for early-life DDT exposure (2007). Given our findings and the suspected role of early-life exposures in thyroid tumor etiology, more work is warranted to better understand the relationship between pesticide exposure during childhood and thyroid cancer.

4.1 Study Strengths and Limitations

A major strength of our study was serum measurement of PCBs and OC pesticides prior to thyroid cancer diagnosis. Furthermore, serum measurements are precise and can, under certain circumstances, approximate lifetime body burden. However, they cannot shed light on the source of OC exposure, or the age at first or peak exposure. Our study was appropriately powered to evaluate OCs and thyroid cancer overall; power for our stratified analyses was more limited. Additionally, analyses stratified by birth cohort assume that measured concentrations at blood collection are correlated with age at first exposure and degree of early-life exposure. We considered that birth cohort may be associated with length of time between blood draw and cancer diagnosis, however these variables were uncorrelated in our data (Spearman ρ=−0.04). We also had estimates of BMI and smoking history and could assess potential confounding by these factors. Nevertheless, we lacked information about other potential confounders, such as ionizing radiation, iodine consumption, and parity (Alcock et al., 2000; Dal Maso et al., 2009). Radioactive fallout from nuclear weapons testing in the 1950s and 1960s may have differentially affected our study population based on geography and birth cohort (Bergan, 2002; Lund and Galanti, 1999). We matched controls on birth date, age at blood draw, and county to minimize potential confounding. Furthermore, we have limited reason to believe OC exposure would be correlated with radiation exposure. Iodine consumption is demonstrated to be protective against follicular thyroid cancer and at very high levels positively associated with papillary thyroid cancer, and like OCs a major dietary source is seafood (Dal Maso et al., 2009; Kvalem et al., 2009). Parity would also have been an informative covariate, as women who breastfeed an infant may experience a 25% decrease in PCB body burden (Alcock et al., 2000), and there is limited evidence to suggest that high parity is associated with increased thyroid cancer risk (Zhu et al., 2016).

Due to the high correlation among PCB congeners within individuals, it was not possible to discern whether our observed associations were due to a single congener, to correlated congeners, or to multiple congeners. PCBs were manufactured as a mixture of many congeners, with the makeup of these mixtures being dependent on the time period and the specific product (IARC, 2016). Individual PCB congeners and their metabolites exhibit a range of mechanistic effects that may be relevant to thyroid cancer development, including formation of DNA adducts, reactive oxygen species, mutagenicity, genotoxicity, competitive binding to numerous receptors, and endocrine disruption (Lauby-Secretan et al., 2016). Though we were not able to examine the effect of multiple PCBs on thyroid cancer in our study due to multicollinearity, exposure to complex PCB mixtures could potentially result in additive or synergistic effects (Langer, 2010).

4.2 Conclusions

In this nested case-control study in Norway, we observed an inverse association between DDT metabolites and thyroid cancer and no overall associations for other OC pesticides and PCBs. However, our findings demonstrating positive associations between specific PCBs and chlordane metabolites for later birth cohorts suggest that early-life exposure to these chemicals may increase risk of thyroid cancer. These results represent the first direct examination of serum OCs and subsequent thyroid cancer, and replication is necessary to

confirm our findings. Future research is warranted to better understand the impact of exposure to persistent organic pollutants over the lifetime and subsequent cancer risk, especially given the persistent nature of these chemicals and ongoing exposure to the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CV	Coefficients of variation
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
HCB	Hexachlorobenzene
HCCH	Hexachlorocyclohexane
LD	Limit of detection
OC	Organochlorine
PCBs	Polychlorinated biphenyls
QC	Quality control
SPE	Solid phase extraction

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Highlights

- First study of pre-diagnostic organochlorine compounds in serum and thyroid cancer
- *p,p′*-DDE (DDT metabolite) inversely associated with thyroid cancer
- Birth cohort may be an effect modifier
- Some PCBs associated with thyroid cancer in youngest birth cohort
- Chlordane metabolites associated with thyroid cancer in youngest birth cohort

Table 1

Characteristics of study participants, stratified by case-control status.

	Thyroid Cancer	Control	
	N=108 N (col%[1])	N=216 N (col%)	p-value[2]
Histopathology[3]			
Papillary	92 (85.2)		
Follicular	14 (13.0)		
Other	2 (1.9)		
Age at diagnosis			
34–50	21 (19.4)		
51–65	52 (48.2)		
66+	35 (32.4)		
Age at blood draw			
18–35	23 (21.3)	41 (19.0)	0.89
36–40	26 (24.1)	57 (26.4)	
41–45	31 (28.7)	67 (31.0)	
46–53	28 (25.9)	51 (23.6)	
Year of blood draw			
1972–1974	37 (34.3)	72 (33.3)	1.00
1975	22 (20.4)	46 (21.3)	
1976–1977	24 (22.2)	48 (22.2)	
1978–1985	25 (23.2)	50 (23.2)	
Birth cohort			
1923–1932	49 (45.4)	98 (45.4)	1.00
1933–1942	37 (34.3)	74 (34.3)	
1943–1957	22 (20.4)	44 (20.4)	
Years from blood draw to diagnosis[4]			
0–10	23 (21.3)	46 (21.3)	0.95
11–20	27 (25.0)	54 (25.0)	
21–30	47 (43.5)	98 (45.4)	
30+	11 (10.2)	18 (8.3)	
Sex			
Male	41 (38.0)	82 (38.0)	1.00
Female	67 (62.0)	134 (62.0)	
County			
Oslo	39 (36.1)	78 (36.1)	1.00
Oppland	27 (25.0)	54 (25.0)	
Sogn og Fjordane	25 (23.2)	50 (23.2)	
Finnmark	17 (15.7)	34 (15.7)	
BMI			
<25	45 (41.7)	98 (45.4)	0.89

	Thyroid Cancer	Control	
	N=108 N (col%[1])	N=216 N (col%)	p-value[2]
25–29.9	30 (27.8)	52 (24.1)	
30+	8 (7.4)	16 (7.4)	
Missing	25 (23.2)	50 (23.2)	
Smoking			
Never smoker	41 (38.0)	63 (29.2)	0.28
Former Smoker	16 (14.8)	30 (13.9)	
Current Smoker	26 (24.1)	72 (33.3)	
Missing	25 (23.2)	51 (23.6)	
Total cholesterol (mg/dL)			
<200	23 (21.3)	45 (20.8)	0.99
200–239	27 (25.0)	53 (24.5)	
240+	58 (53.7)	118 (54.6)	
Total triglycerides (mg/dL)			
<150	50 (46.3)	126 (58.3)	0.08
150–199	23 (21.3)	42 (19.4)	
200+	35 (32.4)	48 (22.2)	

[1] Percentages may not add to 100 due to rounding

[2] Chi-square test for homogeneity

[3] ICD-O-3 Histology codes: Papillary (8050, 8260, 8340–1, 8343–4, 8350), Follicular (8290, 8330–2, 8335)

[4] For controls, time from blood draw to matched case's diagnosis

Table 2

Median and range of selected polychlorinated biphenyl (PCB) and organochlorine (OC) pesticide analytes by thyroid cancer status, and odds ratios (OR) and 95% confidence intervals (95%CI) for thyroid cancer reflecting a 10, 100, or 1000 ng/g change in analyte.

	Thyroid Cancer		Control			
	N	Analyte (ng/g lipid) Median (Range)	N	Analyte (ng/g lipid) Median (Range)	p[1]	OR (95% CI)
Total PCBs[2]	102	971.4 (278.2–3977.8)	205	1075 (199.9–4240.8)	0.10	0.96 (0.90–1.02)
Low-chlorinated[2]	107	67.8 (13.9–673.2)	215	69.9 (15.8–1262.1)	0.61	0.98 (0.76–1.26)
PCB 28[2]	108	19.8 (3.2–468)	216	19.7 (3.8–679)	0.83	1.05 (0.70–1.58)
PCB 74[3]	108	21 (5.8–92)	216	23.5 (1.2–94.3)	0.09	0.85 (0.69–1.05)
Moderately-chlorinated[2]	104	806.4 (230.1–3597.3)	206	919.9 (161.8–3900.7)	0.13	0.95 (0.88–1.02)
PCB 99[3]	108	30.6 (3–120)	216	33.1 (5.4–162)	0.08	0.85 (0.72–1.00)
PCB 105[3]	108	15 (0.4–57.5)	216	16 (0.7–65.7)	0.34	0.83 (0.62–1.12)
PCB 118[3]	108	61.3 (13.2–226)	216	68.7 (14.9–288)	0.30	0.96 (0.89–1.04)
PCB 138/158[2]	108	168 (36.1–689)	216	188.5 (31.7–827)	0.28	0.86 (0.64–1.15)
PCB 146[3]	108	25.6 (8.8–152)	216	28.9 (4.7–169)	0.29	0.94 (0.80–1.11)
PCB 153[2]	108	197.5 (41.2–928)	216	222 (38.7–1120)	0.24	0.91 (0.72–1.14)
PCB 156[3]	108	19.6 (7.3–96.1)	216	21.4 (4.2–84.6)	0.16	0.90 (0.71–1.13)
PCB 170[3]	108	51.6 (22.6–217)	216	56.9 (11.4–214)	0.18	0.96 (0.87–1.05)
PCB 180[2]	108	112.5 (48.9–570)	216	127 (23.5–513)	0.20[k]	0.86 (0.58–1.27)
PCB 183[3]	108	18.2 (2.7–64.8)	216	20.2 (3.7–77.2)	0.30	0.85 (0.64–1.14)
PCB 187[3]	108	39.8 (10.4–204)	216	44.2 (5.9–186)	0.17	0.94 (0.84–1.06)
Highly-chlorinated[3]	107	65.6 (27.4–269.5)	216	71.5 (10.4–274.7)	0.06	0.95 (0.88–1.02)
PCB 194[3]	108	15.5 (6.2–68.1)	216	16.5 (0.5–75.9)	0.18	0.88 (0.67–1.15)
PCB 196/203[3]	108	17.9 (6.2–74.5)	216	19.7 (3.4–69.9)	0.08	0.79 (0.59–1.04)
PCB 199[3]	108	16.6 (6.3–67)	216	17.9 (2.3–77.6)	0.06	0.77 (0.58–1.03)
Thyroid-like[2]	103	179.4 (35.6–945.7)	205	191.0 (44.6–1064.4)	0.33	0.90 (0.69–1.16)

	Thyroid Cancer		Control			
	N	Analyte (ng/g lipid) Median (Range)	N	Analyte (ng/g lipid) Median (Range)	p[1]	OR (95% CI)
Dioxin-like[3]	104	113.1 (36.0–452.5)	206	127.0 (28.7–505.8)	0.16	0.97 (0.92–1.01)
Wolff 1A[3]	107	13.3 (1.8–187.8)	215	13.4 (2.4–423)	0.84	0.98 (0.91–1.06)
Wolff 1B[3]	108	59.9 (15.1–265.1)	216	68.1 (8.9–241.9)	0.13	0.94 (0.86–1.03)
Wolff 2A[2]	108	134.3 (39.1–524.7)	216	152.8 (34.2–592.1)	0.15	0.80 (0.55–1.16)
Wolff 2B[2]	108	224.3 (59.9–915.6)	216	247.1 (43.8–1069.8)	0.24	0.89 (0.71–1.11)
Wolff 3[2]	108	364.3 (102.8–1675.2)	216	403.3 (71–1857.7)	0.17	0.94 (0.82–1.07)
OC Insecticides						
DDT Metabolites[4]	104	1630.3 (93–6793.6)	209	1845.5 (145–11511.4)	0.09	0.80 (0.66–0.98)
p,p′-DDE[4]	104	1445 (67.6–6000)	209	1630 (123–10800)	0.08	0.79 (0.64–0.97)
p,p >-DDT[2]	108	166.5 (12.5–762)	216	198 (10.8–1450)	0.18	0.86 (0.71–1.05)
o,p′-DDT[3]	108	11 (2–75.3)	216	13.3 (2.1–115)	0.13	0.81 (0.64–1.02)
Chlordane Metabolites[3]	108	28.4 (4.1–134.9)	215	31.1 (6.5–168.6)	0.32	0.92 (0.80–1.06)
trans-nonachlor[3]	108	16.8 (2.1–86.7)	216	18.8 (3.7–97)	0.44	0.89 (0.71–1.11)
β-HCCH[2]	106	65.5 (1.8–452)	214	74.2 (2.5–3320)	0.06	0.62 (0.33–1.16)
HCB[2]	106	173 (27.7–667)	214	194 (11.1–2250)	0.10	0.76 (0.54–1.06)

Abbreviations: dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), hexachlorocyclohexane (HCCH), hexachlorobenzene (HCB)

[1] Wilcoxon rank sum test

[2] OR reflects 100-unit change

[3] OR reflects 10-unit change

[4] OR reflects 1000-unit change

Table 3

Selected odds ratios (OR) and 95% confidence intervals (95%CI) for thyroid cancer reflecting a 10, 100, or 1000 ng/g change in analyte, stratified by birth cohort.

	Stratified by Birth Cohort			
	1923–1932 49 cases, 98 controls	1933–1942 37 cases, 74 controls	1943–1957 22 cases, 44 controls	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	$P_{interaction}$
Total PCBs[1]	0.92 (0.83–1.01)	0.94 (0.86–1.03)	1.25 (1.00–1.56)	0.04
Low-chlorinated[1]	0.53 (0.23–1.21)	1.15 (0.81–1.63)	0.87 (0.49–1.56)	0.21
PCB 28[1]	0.20 (0.03–1.49)	1.29 (0.78–2.14)	0.78 (0.26–2.32)	0.17
PCB 74[2]	0.77 (0.57–1.05)	0.90 (0.63–1.27)	1.33 (0.62–2.85)	0.42
Moderately-chlorinated[1]	0.91 (0.81–1.02)	0.92 (0.82–1.03)	1.31 (1.01–1.70)	0.04
PCB 99[2]	0.78 (0.61–0.99)	0.86 (0.65–1.14)	1.57 (0.82–3.01)	0.14
PCB 105[2]	0.81 (0.55–1.20)	0.63 (0.34–1.17)	4.26 (0.96–19.0)	0.07
PCB 118[2]	0.94 (0.85–1.05)	0.92 (0.80–1.07)	1.28 (0.97–1.71)	0.11
PCB 138/158[1]	0.73 (0.46–1.15)	0.78 (0.48–1.25)	4.54 (1.20–17.2)	0.04
PCB 146[2]	0.85 (0.65–1.11)	0.92 (0.73–1.16)	2.48 (1.10–5.58)	0.05
PCB 153[1]	0.75 (0.50–1.12)	0.88 (0.63–1.22)	3.47 (1.18–10.2)	0.03
PCB 156[2]	0.75 (0.50–1.11)	0.87 (0.62–1.23)	2.16 (0.93–5.01)	0.08
PCB 170[2]	0.88 (0.75–1.05)	0.94 (0.82–1.06)	1.35 (0.98–1.85)	0.07
PCB 180[1]	0.59 (0.28–1.24)	0.79 (0.46–1.37)	3.43 (0.92–12.7)	0.07
PCB 183[2]	0.74 (0.47–1.15)	0.73 (0.45–1.19)	4.00 (1.20–13.3)	0.03
PCB 187[2]	0.85 (0.69–1.04)	0.94 (0.80–1.11)	1.45 (0.94–2.23)	0.09
Highly-chlorinated[2]	0.87 (0.75–1.00)	0.95 (0.86–1.06)	1.10 (0.92–1.33)	0.13
PCB 194[2]	0.72 (0.43–1.20)	0.86 (0.58–1.27)	1.28 (0.68–2.43)	0.38
PCB 196/203[2]	0.55 (0.33–0.92)	0.81 (0.54–1.22)	1.57 (0.77–3.20)	0.06
PCB 199[2]	0.53 (0.31–0.90)	0.84 (0.56–1.24)	1.26 (0.65–2.43)	0.12
Thyroid-like[1]	0.62 (0.38–1.02)	1.01 (0.73–1.40)	1.83 (0.63–5.28)	0.11
Dioxin-like[2]	0.95 (0.88–1.02)	0.94 (0.86–1.03)	1.16 (0.98–1.38)	0.07
Wolff 1A[2]	0.96 (0.80–1.16)	1.01 (0.91–1.12)	0.96 (0.82–1.12)	0.83
Wolff 1B[2]	0.91 (0.79–1.05)	0.93 (0.81–1.06)	1.19 (0.89–1.61)	0.26
Wolff 2A[1]	0.71 (0.42–1.20)	0.70 (0.36–1.36)	4.05 (0.85–19.2)	0.10
Wolff 2B[1]	0.78 (0.54–1.11)	0.83 (0.58–1.18)	2.92 (1.11–7.69)	0.04
Wolff 3[1]	0.83 (0.66–1.05)	0.92 (0.76–1.11)	1.80 (1.04–3.12)	0.04
OC Pesticides				
DDT Metabolites[3]	0.69 (0.49–0.98)	0.89 (0.66–1.20)	0.87 (0.57–1.31)	0.53
p,p′-DDE[3]	0.66 (0.45–0.97)	0.88 (0.64–1.21)	0.87 (0.56–1.35)	0.49

	Stratified by Birth Cohort			
	1923–1932 49 cases, 98 controls	1933–1942 37 cases, 74 controls	1943–1957 22 cases, 44 controls	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	$P_{interaction}$
p,p′-DDT[1]	0.84 (0.63–1.13)	0.96 (0.68–1.36)	0.74 (0.41–1.33)	0.72
o,p′-DDT[2]	0.79 (0.57–1.09)	0.90 (0.62–1.29)	0.72 (0.37–1.37)	0.79
Chlordane Metabolites[2]	0.81 (0.65–1.02)	0.88 (0.69–1.13)	1.78 (1.09–2.93)	0.02
trans-Nonachlor[2]	0.68 (0.47–0.98)	0.90 (0.61–1.31)	2.43 (1.11–5.34)	0.02
β-HCCH[1]	0.28 (0.09–0.88)	0.94 (0.45–1.95)	0.82 (0.24–2.81)	0.21
HCB[1]	0.63 (0.36–1.08)	0.90 (0.54–1.48)	0.87 (0.31–2.43)	0.62

Abbreviations: dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), hexachlorocyclohexane (HCCH), hexachlorobenzene (HCB)

[1] OR reflects 100-unit change

[2] OR reflects 10-unit change

[3] OR reflects 1000-unit change