BREAST CANCER AMONG ALASKA NATIVE WOMEN POTENTIALLY EXPOSED TO ENVIRONMENTAL ORGANOCHLORINE CHEMICALS

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ABSTRACT

Objectives. To determine if an increased rate of breast cancer in Alaska Native women is related to their consumption of a subsistence diet that may contain p,p'-dichlorodiphenylethylene (DDE) and polychlorinated biphenyls (PCBs).

Study Design. A retrospective case control design.

Methods. We analyzed banked serum collected between 1981 and 1987 from 126 Alaska Native women, including 63 case women who subsequently developed breast cancer and 63 age-matched control women who remained cancer-free. Serum was analyzed for DDT, DDE, 13 other chlorinated pesticides, and 28 PCB congeners.

Results. The geometric mean for p,p’-DDE levels among case women was 8.67 ppb (95% Confidence Interval 7.48, 10.04); among control women, the geometric mean was 7.36 ppb (6.53, 8.30). The geometric mean for total PCB levels among case women was 4.55 ppb (3.61, 5.74) and for control women, the geometric mean was 6.10 ppb (4.73, 7.86). Cancer status and total PCB levels varied across ethnicity (i.e., Eskimo, Aleut, and Indian) but DDE levels were uniform among these ethnic groups. Using conditional logistic regression analysis to adjust for potential confounders (e.g., ethnicity, family history of breast cancer, parity), we found an odds ratio of 1.43 (0.46, 4.47) for the highest tertile of DDE exposure and 0.42 (0.07, 2.38) for the highest tertile of total PCB exposure.

Conclusions. Although the results are limited by small sample size and restricted risk factor information, our findings of higher DDE levels, but lower PCB levels among women with breast cancer are consistent with previous research. Our results confirm exposure to organochlorines among Alaska Native women but do not identify these exposures as a significant risk factor for breast cancer.

Keywords: breast cancer, Alaska Natives, organochlorines, persistent organic pollutants, environmental pollution
INTRODUCTION

Many studies have explored the relationship between breast cancer and exposure to organochlorine chemicals (1-22), but only a subset has focused on women with on-going exposure (1, 6-8, 10, 12, 18). Alaska Natives may be uniquely exposed by consuming a subsistence diet of marine mammals which bioaccumulate organochlorines (23-29). Alaska Native women have manifested a three-fold increase in breast cancer since the early 1970s when their rate of breast cancer was half the rate of white women in the United States (30). By 1998, the rates for both groups of women were nearly equal (30, 31). From 1999-2003, the breast cancer rate among Alaska Native women was not statistically different than the rate among white women in the United States (A. Lanier, emailed personal communication, November 28, 2005). Although the increased incidence in breast cancer among Alaska Native women may be partially due to increased availability of mammography, this has only been widely available since the 1990s. The increased trend in breast cancer cases began as early as 1969 (30). Due to potential exposure to persistent organic pollutants (POPs) and the rapid increase in cancer rates, the relationship between breast cancer and organochlorines within this population merited investigation.

This paper presents the results of a case-control study of breast cancer among Eskimo, Aleut, and Indian women in Alaska. We used banked serum samples to measure levels of p,p'-dichlorodiphenyltrichloroethane (DDT) and its breakdown product, p,p'-dichlorodiphenyltrichloroethylene (DDE), polychlorinated biphenyls (PCBs) and other chlorinated pesticides, and we reviewed medical records for breast cancer risk factors identified in other studies. The project was a collaborative effort by the Centers for Disease Control and Prevention’s (CDC) National Center for Environmental Health (NCEH), the Alaska Native Tribal Health Consortium (ANTHC), and the National Cancer Institute.

METHODS

Study design
We identified breast cancer patients from the Alaska Native Tumor Registry (ANTR), starting with incident cases for 1995 and working back in time. The ANTR has actively enrolled Alaska Natives diagnosed with cancer statewide since 1969. It includes Alaska Natives eligible for Indian Health Services (IHS) and resident in Alaska at the time of diagnosis. We enrolled women from the registry diagnosed with breast cancer who also had serum stored in the Arctic Investigations Serum Bank (AISP). This serum bank was established in the 1950s as a collaborative effort between CDC and IHS. More than 95% of Alaska Natives have at least one serum sample in the AISP.

Our goal was to identify 60 case women. We screened each potential case woman to determine if she had a banked serum sample collected 3 to 10 years before the date of cancer diagnosis. Each potential case woman was further screened for the availability of a retrievable medical record through the Alaska Native Medical Center (ANMC) in Anchorage, the tertiary medical service provider for all Alaska Natives statewide. Sixty-three women with sufficient available serum and accessible risk-factor information were identified.
For each case woman, we identified an eligible control subject from the serum bank. Controls were selected if their age was within five years of a case and they also had a serum sample collected the same year as the case. Control women were also required to have a medical chart available for review at ANMC and to be alive and without cancer diagnosis at the date of case diagnosis.

Our study included 63 women with breast cancer and 63 women who were cancer free. All selected serum samples had been collected between 1981 and 1987. The level of detail of the data we were able to abstract from the medical charts at the ANMC was limited by Institutional Review Board confidentiality criteria. Variables collected included age group (45-54 years or >54 years), ethnicity (Eskimo, Indian, or Aleut), geographic region of residence at birth and at diagnosis (southcentral, northwestern, south-western, or interior), parity (yes/no), age at menarche (< 12 years or >12 years), family history of breast cancer (yes/no), and for case women, tumor hormonal receptor status (estrogen and progesterone positive or negative). Serum samples were analyzed for DDT, DDE, 13 other chlorinated pesticides, and 28 PCB congeners.

Laboratory analysis
Serum samples were analyzed at the Division of Environmental Health Laboratory Science, NCEH, CDC. A reagent blank and a quality-control sample were added to each batch of 10 submitted samples. Each sample was extracted using solid-phase extraction and then analyzed on two separate gas chromatographs with electron capture detection. The two chromatographs used different columns (DB5 and DB1701) to reduce interferences and improve selectivity. Results were obtained for o,p’-DDE, p,p’-DDE, o,p’-DDT, p,p’-DDT, 28 PCB congeners, and 13 other organochlorine compounds using previously described methods (32). These methods allowed for values below the established level of detection to be detected.

Serum samples were analyzed for cholesterol and triglycerides on a Kodak Ektachem 250 Dry Chemistry Analyzer (Ortho Clinical Diagnostics, Rochester, NY), and total lipids were calculated using a standard formula (33). A lipid-adjusted total PCB variable was created by summing all congener values and dividing by total lipids. The intraset coefficient of variations (C.V.) was 8.5% and the interset C.V. was 13%. All results were recovery corrected; data were furnished both with and without lipid adjustment (units ng/g lipid or ppb-lipid adjusted or ng/ml or ppb unadjusted, respectively).

Statistical analysis
All data were used without screening for the formal method detection limit (LOD) (32). We used the analytical LOD that eliminates 95% of false positives to identify those analytes that were detectible in more than 50% of our study population. Analytes with less than 50% detection were not studied individually; all congeners were considered in calculating total PCB.

We conducted all analyses using recovery-corrected analytical results, initially using lipid unadjusted values and then repeating using lipid-adjusted values; lipid adjustment did not alter our results. We assessed the distribution of demographic variables, potential risk factors for breast cancer, and
We identified the analytes that were detectable in at least 50% of the 126 serum samples and calculated geometric means, confidence intervals, and medians according to case-control status. We used conditional logistic regression to investigate the relationship between breast cancer, DDE, and total PCBs. We ran the models using both continuous and categorical values for the analytes. In the latter instance, each model included dummy variables that were based on control-group tertile values. We included the unadjusted analyte values and the lipid-adjusted values in separate models. Additional variables included ethnicity, family history of breast cancer, parity, and age at menarche. We calculated odds ratios (OR) and 95% confidence intervals (CI) and also tested for trend. The conditional logistic regression models for DDE and total PCB were repeated among the estrogen receptor positive case women and their matched control women.

RESULTS

Sixty-four percent of the study participants were older than 54 years of age. The majority of women were Eskimo (64%), followed by Aleut (19%) and Indian (17%) (Table I). This ethnic distribution is consistent with ethnic distribution reported in the Alaska Census (34). In our study population control women were more likely to be Eskimo; 53 (65%) of 81 Eskimo women in the study were controls in comparison to 28 (35%) case women who were Eskimo. The majority of Aleut (76%) and Indian participants (79%) were cases. Ethnicity was highly correlated with region at birth and region at diagnosis (p<0.001). For more than 90% of the women, region at birth was the same as region at diagnosis. Control women were more likely to have been born in the southwestern region while no controls were drawn from the interior region. Median serum triglyceride values also differed significantly (p<0.001) between case and control women however no significant differences existed for parity, age of menarche, family history of breast cancer, and median cholesterol.

We looked at the entire study population to determine if age, parity (as a surrogate for lactation), ethnicity or region at birth was associated with organochlorine levels. We found that DDE and total PCB serum levels were higher in the older age group and among nulliparous women. Those women with unknown parity had levels similar to those who had given birth at least once. DDE levels were similar across ethnicity and region at birth while total PCB levels varied across both variables. Total PCB levels were highest among Eskimo women (6.54 ppb) and lowest among Indian women (2.55 ppb). The levels were almost twice as high among those women born in the northwestern and southwestern regions as the levels in women born in the southcentral and interior regions (Table II).

Five analytes including DDE, hexachlorobenzene, trans-nonachlor, oxychlordane, and dieldrin were detected in more than 50% of the 126 samples. The percentage of women with detectable levels was similar for cases and controls. The geometric mean
and median level of four of the five detected analytes differed significantly between cases and controls (Table III). The geometric mean for p,p′-DDE levels among women with breast cancer was 8.67 ppb (7.48, 10.04); among control women the geometric mean was 7.36 ppb (6.53, 8.30). For total PCBs, the geometric mean and median levels were significantly lower for cases than controls. The geometric mean for total PCB levels was 4.55 ppb (3.61, 5.74) (median 5.3) for case women and 6.10 ppb (4.73, 7.86) (median 8.08) for control women.

Table I. Distribution of demographic variables, selected risk factors, and serum lipid levels by case-control status among Alaska Native women. Total column indicates the number of women in the total study population (n = 126) for whom information was available for a given descriptive variable.

| Variable                        | Total (%) | Case (%) | Control (%) | p value |
|---------------------------------|-----------|----------|-------------|---------|
| Ethnicity                       | n = 126   | n = 63   | n = 63      | < 0.001 |
| Eskimo                          | 81 (64.3) | 28 (44.4)| 53 (84.2)   |         |
| Aleut                           | 21 (16.7) | 16 (25.4)| 5 (7.9)     |         |
| Indian                          | 24 (19)   | 19 (30.2)| 5 (7.9)     |         |
| Geographic region at birth      | n = 121   | n = 61   | n = 60      | < 0.001 |
| Southcentral                    | 33 (27.3) | 26 (42.6)| 7 (11.7)    |         |
| Northwestern                    | 31 (25.6) | 15 (24.6)| 16 (26.7)   |         |
| Southwestern                    | 52 (43.0) | 15 (24.6)| 37 (61.7)   |         |
| Interior                        | 5 (4.1)   | 5 (8.2)  | 0           |         |
| Family history (Y/N)            | n = 111   | n = 60   | n = 51      | 0.06    |
| yes                             | 11 (9.9)  | 9 (15.0) | 2 (4.0)     |         |
| Nulliparous (Y/N)               | n = 108   | n = 52   | n = 56      | 0.10    |
| yes                             | 6 (5.6)   | 5 (9.6)  | 1 (1.8)     |         |
| Menarche < / > 12ys             | n = 64    | n = 34   | n = 30      | 0.65    |
| < 12 years                      | 21 (32.8) | 12 (35.3)| 9 (30.0)    |         |
| Median cholesterol              | 124       | 182 mg dl⁻¹ | 212 mg dl⁻¹ | 0.01    |
| Median triglycerides            | 125       | 150 mg dl⁻¹ | 104 mg dl⁻¹ | < 0.001 |

\( ^a \chi^2 \text{ test} \)

\( ^b \) Fisher’s exact test

\( ^c \) Wilcoxin signed rank test

Table II. Median levels (95% CI) of DDE and total PCBs among 126 case and control Alaska Native women, according to demographic variables.

| Variable                        | DDE (95% CI) | PCBs (95% CI) |
|---------------------------------|--------------|---------------|
| Age 45-54 years                 | 9.60 (6.28, 8.74) | 5.44 (4.08, 6.84) |
| Age > 54 years                  | 9.30 (7.86, 10.51) | 6.72 (5.32, 9.45) |
| Parity unknown                  | 7.92 (4.88, 10.80) | 6.99 (2.91, 8.86) |
| One or more children            | 8.42 (7.45, 9.79) | 5.87 (4.59, 8.08) |
| Nulliparous                     | 12.70 (7.87, 20.31) | 9.57 (1.99, 28.64) |
| Eskimo                          | 8.56 (6.58, 9.63) | 8.57 (5.92, 10.00) |
| Aleut                           | 9.30 (6.32, 11.61) | 5.61 (2.21, 7.62) |
| Indian                          | 8.37 (7.45, 10.51) | 2.96 (1.16, 5.99) |
| Born southcentral               | 8.30 (7.60, 10.26) | 4.29 (1.80, 5.85) |
| Born northwestern               | 6.73 (6.01, 9.96) | 7.60 (4.08, 13.38) |
| Born southwestern                | 8.85 (6.41, 10.67) | 8.13 (5.44, 9.94) |
| Born interior                   | 9.47 (3.10, 10.74) | 5.21 (2.64, 8.54) |
A univariate analysis revealed a non-significant increased risk for breast cancer among women in the highest tertile of DDE exposure. The non-significant risk was also found in a multivariate analysis that included ethnicity, family history of breast cancer, parity, and levels of triglycerides and cholesterol. Additional multivariate analyses using estrogen-receptor positive women and control women produced a crude OR_{T1-T2} for DDE of 0.77 (0.28, 2.11) and a crude OR_{T2-T3} of 1.76 (0.66, 4.68) but failed to identify a significant increased risk (Table IV). A significant decreased risk for breast cancer across tertiles of total PCB levels was found in a univariate analysis; however the trend was no longer significant in the multivariate analysis (Table IV). DDE and total PCB levels among control women

### Table III Persistent organic analytes with > 50% detection in 126 Alaska Native women by breast cancer status (63 case and 63 age-matched control women).

| Analyte                 | % detection | Median ppb (95% CI) | p value a |
|-------------------------|-------------|---------------------|-----------|
| DDE                     | 99.2        | case women 98.4     | 9.43 (7.60, 10.80) | 0.02     |
|                         |             | control women 100   | 7.86 (6.32, 8.96)  |
| Hexachlorobenzene       | 98.4        | case women 96.8     | 1.49 (1.10, 1.94)  |
|                         |             | control women 100   | 2.63 (2.19, 3.67)  | 0.005    |
| Trans-nonachlor         | 70.6        | case women 61.9     | 0.39 (0.13, 0.67)  |
|                         |             | control women 79.4  | 0.77 (0.65, 1.35)  | 0.004    |
| Oxychlordane            | 58.7        | case women 55.6     | 0.29 (0.09, 0.47)  |
|                         |             | control women 61.9  | 0.53 (0.09, 0.79)  | 0.004    |
| Dieldrin                | 50.8        | case women 54       | 0.23 (0.11, 0.34)  |
|                         |             | control women 47.6  | 0.11 (0.11, 0.33)  | 0.8      |

a Wilcoxon signed rank test of the null hypothesis that median difference among pairs = 0

### Table IV Odds Ratio for breast cancer according to tertile of serum DDE and PCB levels among Alaska Native women with samples collected from 1983-1987.

| ppb of DDE | Tertile 1 | Tertile 2 | Tertile 3 | p value for trend |
|------------|-----------|-----------|-----------|-------------------|
| Case women (n) | 15 | 18 | 30 | 0.13 |
| Control women (n) | 21 | 21 | 21 | 0.43 |

Univariate

| Odds Ratio (95% CI) | 1.14 (0.48, 2.71) | 1.87 (0.82, 4.27) | 0.13 |

Multivariate a

| Odds Ratio (95% CI) | 0.57 (0.15, 2.19) | 1.43 (0.46, 4.47) | 0.43 |

### ppb of PCBs

| Tertile 1 | Tertile 2 | Tertile 3 | p value for trend |
|------------|-----------|-----------|-------------------|
| Case women (n) | 33 | 20 | 10 | 0.005 |
| Control women (n) | 21 | 21 | 21 | 0.32 |

Univariate

| Odds Ratio (95% CI) | 0.34 (0.11, 1.09) | 0.13 (0.03, 0.54) | 0.42 (0.07, 2.38) | 0.32 |

Multivariate a

| Odds Ratio (95% CI) | 0.56 (0.11, 2.74) | 0.42 (0.07, 2.38) | 0.32 |

a Adjusted for parity, family history of breast cancer, ethnicity, and triglycerides and cholesterol levels.
were evaluated to determine if variable interactions existed between ethnicity, region at birth, parity, age of menarche, family history of breast cancer, cholesterol, and triglyceride levels. Control women with serum levels above the median were compared with those below the median. No significant variable interactions were found.

DISCUSSION

Our study was a pilot investigation to evaluate the relationship between organochlorine levels and subsequent breast cancer diagnosis. We found significantly higher geometric mean and median levels of DDE in case women but significantly lower levels of hexachlorobenzene, trans-nonachlor, and oxychlordane. In addition, case women also had significant lower levels of total PCBs. Conditional logistic regression analysis did not reveal significant associations between DDE or PCB levels and breast cancer when adjusted for other risk factors.

Early studies reporting an association between DDE serum levels and breast cancer (19, 35-37) have not been uniformly replicated by subsequent larger research studies (4, 5, 9-11, 14, 21, 38). Four recent studies involving non-white or non-Western populations of women found significantly higher DDE levels among women with breast cancer (1, 16, 39, 40). These populations of women live in countries where the use of DDT is not banned or has only recently been banned; therefore exposure is likely to be greater and on-going. These women may be better suited for studying the relationship between DDT, DDE, and breast cancer (41).

Our finding of higher PCB levels among control women is consistent with recent studies (9, 10, 16, 35, 38, 42) that have failed to find the significant association between PCBs and breast cancer that was described in earlier research (19, 36, 43). Increasing evidence suggests that PCBs may actually exert congener-specific effects that vary from estrogenic to anti-estrogenic (44-46), and future research should consider the effects of PCB congeners individually. A few studies have associated high levels of PCB congeners 183, 170, 180, and 28 with an increase in risk for breast cancer (2, 47-49) while congeners 153 and 156 were shown to have a protective effect in a New Haven, CT investigation (47). In our study all congener-specific PCB levels, like the total PCB level, were higher among control women.

Our findings of higher PCB levels among Eskimo women and among women born and living in the northwestern and southwestern regions may reflect PCB profiles within their marine mammal subsistence food. Likewise, lower PCB levels among Indian women and women born in the interior region may be a reflection of a diet consisting of less marine mammals (50, 51). However, cancer data from the ANTR documents that certain Indian ethnic groups have a much higher incidence of breast cancer than other Alaska Native women (52).

Our results are limited by small sample size and requirements to aggregate risk-factor variable information. In order to address the sample size limitations and increase the power of our findings, we refined our population selection methods by age-matching controls to cases in 5-year age groupings. Due to confidentiality restrictions, we were
not able to use the age-matched categories or to collect first hand risk factor information. The restrictions ultimately led us to combine age groups into categories above and below 54 years, and menopausal status was determined from the medical chart. The lack of information obtained about potential risk factors for breast cancer from medical records decreased our ability to conduct detailed conditional logistic regression modeling which might have increased the precision of our results.

Despite the limitations, this study was able to control for selected risk factors for breast cancer (i.e., family history and parity) in multivariate models (53). Both older women (who have more years of exposure) and nulliparous women (who don’t have the opportunity to decrease their organochlorine body burden through lactation) are more likely to have higher serum organochlorine levels. Confirmation of these expected relationships between the level of organochlorine exposure and a woman’s age group and parity status supports the quality of our medical chart review information about breast cancer risk factors. Even though our results do not provide strong support for the relationship between organochlorines and breast cancer, our findings do provide useful information about historical levels of organochlorines in this subpopulation.

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