

# Cancer Incidence Among Capacitor Manufacturing Workers Exposed to Polychlorinated Biphenyls

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**Background** We evaluated cancer incidence in a cohort of polychlorinated biphenyl (PCB) exposed workers.

**Methods** Incident cancers, identified using state registries, were compared to those in a national population using standardized incidence ratios. Trends in prostate cancer incidence with cumulative PCB exposure were evaluated using standardized rate ratios and Cox regression models. For selected sites, cumulative PCB exposure was compared between aggressive (fatal/distant stage) and localized/regional cancers.

**Results** We identified 3,371 invasive first primary cancer diagnoses among 21,317 eligible workers through 2007. Overall relative incidence was reduced. Elevations were only observed for respiratory cancers and among women, urinary organ cancers. Among men, prostate cancer incidence was reduced and not associated with cumulative PCB exposure although median exposures were significantly higher for aggressive compared to localized/regional prostate cancers.

**Conclusion** Previously observed associations between cumulative PCB exposure and prostate cancer mortality were not confirmed in this analysis; prostate cancer stage at diagnosis may explain the discrepancy. Am. J. Ind. Med. 60:198–207, 2017. Published 2016. This article is a U.S. Government work and is in the public domain in the USA.

**KEY WORDS:** prostate neoplasms; cancer incidence; polychlorinated biphenyls; occupational exposure

## INTRODUCTION

Cohort mortality studies have long been a mainstay of occupational cancer epidemiology. However, for cancer sites with high survivability, mortality studies may not be the best way to investigate the relation between exposure to a carcinogen and the risk of cancer [Boyle, 1989].

The National Institute for Occupational Safety and Health (NIOSH) polychlorinated biphenyl (PCB) cohort includes 24,865 capacitor-manufacturing workers exposed to PCBs from 1938 to 1977 at plants in Indiana, Massachusetts, and New York. For several a priori sites, including prostate cancer, a mortality update showed significant exposure–response relations between exposure and mortality [Ruder et al., 2014]. Among long-term workers ( $\geq 90$  days of employment), prostate cancer mortality (78 deaths) was significantly associated with cumulative PCB exposure and was significantly elevated (25 deaths, standardized rate ratio [SRR] 2.11, 95% confidence interval [CI] 1.08–4.13) in the highest ( $\geq 600,000$  unit-days) relative to the lowest ( $< 40,000$  unit-days) exposure category [Ruder et al., 2014].

To determine if prostate cancer incidence in the NIOSH PCB cohort would parallel our cancer mortality findings, we conducted a cancer incidence study on this cohort using data from cancer registries in the three study states and six additional states to which substantial numbers of cohort

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members had moved. We focused on prostate cancer, based on our mortality study results and its high survivability (~100% 5-year survival and 99% 10-year survival) [American Cancer Society, 2013], but we evaluated all sites for both sexes.

## METHODS

Details about cohort enumeration and mortality are presented in detail elsewhere [Ruder et al., 2014] and briefly here. The cohort includes everyone with complete demographic information employed at the study facilities for 1 day or more while PCBs were in use ( $n = 24,865$ ). To ascertain vital status, worker data were linked to the Social Security Administration and the National Death Index (NDI). Causes of death were obtained from NDI Plus for deaths in 1979 or later; for earlier deaths, death certificates were obtained from state vital statistics offices and coded to the International Classification of Diseases revision in effect at the time of death.

All workers were matched to cancer registries in New York, Massachusetts, and Indiana, with complete ascertainment beginning in 1976, 1982, and 1987, respectively. To minimize losses due to migration, we also matched workers to cancer registries in Connecticut, Rhode Island, California, Texas, Florida, and North Carolina, with complete ascertainment beginning in 1973, 1986, 1988, 1995, 1997, and 1999, respectively. Registries provided matching through December 31, 2007. After excluding workers who had died ( $n = 1306$ ) or were lost to follow-up ( $n = 656$ ) before their respective cancer registries were operating, 22,903 workers were initially eligible for the primary cancer incidence analysis (10,693 male workers for the prostate cancer analysis). Through 2007, 7,006 (31%) of the eligible workers had died with 6,055 (86%) of these deaths occurring in the registry states (Supplemental File, Table SI).

Cancer registries provided date of diagnosis and International Classification of Diseases for Oncology Third Edition (ICD-O-3) codes for primary site, laterality, morphology, and stage. Incident cases (all primary invasive cancers and in situ bladder cancers) were classified into 12 major and 41 minor cancer incidence groupings (Supplemental File, Table SII). Diagnosis dates were assigned as January 1st if only the year was known, and on the 1st of the month if only the month and year were known. For prostate cancer, the rate of case under-ascertainment by using death certificates to identify cases was estimated using methods in Freedman et al. [2006]. For analysis of first primary invasive cancer, we excluded workers diagnosed before their respective cancer registries were operating. For analysis of prostate cancer, we excluded men with prostate cancer diagnoses before their respective cancer registries were operating, but not men with other cancer diagnoses.

Historical address information was used to estimate when workers first entered and first left the time-dependent catchment area (hereafter “the catchment”). The catchment first encompassed Connecticut from 1973 to 1975. New York joined the catchment in 1976; over time the catchment was enlarged until for 1999–2007 it included all nine states. Available address information was combined to form a residence history for each worker (see Supplemental File, Additional details on state of residence). For a given year, workers were considered to be in the catchment if living in any state associated with the catchment. Workers thought to never have lived in the catchment were excluded. Workers leaving the catchment before the study end date contributed person-years at risk (PYAR) until they left. Although some workers may have returned to the catchment, the primary analysis (described below) only considered the initial risk period.

Detailed work history records included begin date, end date, department, and job title. Plant-specific job exposure matrices were used to assign exposure scores for inhalation and dermal exposure to PCBs [Hopf et al., 2009, 2010, 2014]. An un-weighted average of inhalation and dermal exposure scores was used to estimate cumulative exposure (the product of the number of days in each department and job-title and the assigned score, summed over all jobs worked), which was expressed as unit-days or -years.

Cohort cancer rates were compared to rates in the Surveillance, Epidemiology, and End Results (SEER) referent population, which covers approximately 28% of the US population [Howlander et al., 2014] using standardized incidence ratios (SIRs) from a life-table analysis program (LTAS.NET) [Schubauer-Berigan et al., 2011]. In this analysis, the numerator was based on first primary invasive cancers among eligible cohort members. Analyses of the first primary invasive cancer (overall and site-specific) used SEER 1976–2009 rates adjusted for cancer prevalence [Merrill et al., 2012]. SIRs were also used to compare prostate cancer rates among male workers to the SEER referent population; in this analysis, the first primary prostate cancer was considered (and other earlier cancers were ignored) and reference rates were based on SEER data (1976–2006) unadjusted for cancer prevalence (i.e., all prostate cancers were considered).

For each worker, the date risk began was the later of the date of first employment and the date the worker entered the catchment. The date risk ended was the earliest of the date of diagnosis (cases), the date last observed (workers lost to follow-up), the date of death (deceased workers), the date the worker left the catchment (if applicable), and the study end date (workers alive, cancer free, and still in the catchment on 12/31/2007). Person-time at risk was stratified by age and calendar year (in 5-year categories) and multiplied by gender- and race-specific cancer incidence rates to obtain expected numbers of cases. The SIR was defined as the ratio

of the observed to the expected numbers of cases and 95% CIs were estimated under the assumption of a Poisson distribution. Race was unknown for over half of the cohort [Ruder et al., 2014]; White race was assumed when unknown based on plant locations.

The primary analysis used cancer registry data to identify cases and registry states to define the catchment. Sensitivity analyses for prostate cancer explored different scenarios: limiting the catchment to the three plant states and limiting cases to those identified using these registries; additionally including cases identified using death certificates from the nine registry states; including all risk periods (i.e., all person-time at risk in the catchment contributed to the denominator); assigning the earlier state to the entire gap in the residence history; assigning the later state to the entire gap; and excluding nine “lost and found” workers. Additional details of these sensitivity analyses are provided (Supplemental File, Sensitivity Analyses).

Prostate cancer incidence was compared by plant state (Indiana, Massachusetts, and New York) and by employment duration (<90 days, 90+ days) (Supplemental File, External analyses). Standardized rate ratios and Cox proportional hazards regression models were used to evaluate associations between prostate cancer incidence and cumulative PCB exposure (Supplemental File, Internal analyses).

Finally, we conducted a post hoc analysis comparing cumulative PCB exposure for aggressive prostate cancer diagnoses to indolent prostate cancer diagnoses, using the definition of Koutros et al. [2013] that aggressive prostate cancers were fatal (underlying cause prostate cancer) or distant stage at diagnosis. Lacking another metric, we applied this definition across cancer sites, and defined an aggressive cancer as fatal (with the underlying cause of death being the same cancer) or distant stage at diagnosis. Because the distribution of cumulative PCB exposure was highly right-skewed, we compared median exposures for aggressive cases to indolent cases (localized or regional stage at diagnosis) using the Wilcoxon two-sample test.

This study (HSRB-08-DSHEFS-02) was approved by the NIOSH Human Subjects Review Board and participating state cancer registries. As a records study, it was exempted from informed consent requirements.

## RESULTS

Among eligible workers 4,084 invasive cancer diagnoses occurred; all after the workers began employment. With only a few exceptions ( $n = 8$ ), all diagnoses occurred after the workers ended employment. We excluded 121 duplicate matches and 304 later diagnoses among workers with multiple primary diagnoses (for 21 workers with multiple primary tumors on the same day, we selected the most common cancer); 33 workers diagnosed before their

respective cancer registry began operation; 1,507 workers (53 diagnoses) with no time in the catchment; and 46 workers diagnosed before entering the catchment. We censored PYAR for 2,244 workers who left the catchment before the study end date (and ignored 156 subsequent diagnoses in this group).

Cancer case and non-case demographics are in Table I. For the analysis of first primary invasive cancer, 3,371 cases were observed among 21,317 workers contributing 427,511.2 PYAR. Cancer incidence was significantly reduced (SIR 0.93, 95%CI 0.90–0.96) (Table II). Significant elevations were observed for respiratory cancers overall (SIR 1.23, 95%CI 1.14–1.33) and urinary organ cancers among females (SIR 1.27, 95%CI 1.01–1.53).

For the prostate cancer analysis, we considered all prostate cancer matches ( $n = 501$ ) regardless of other diagnoses. We excluded three duplicate matches and one second primary match; three workers with prostate cancer diagnoses before their respective cancer registry began operation; 776 workers (five diagnoses) with no time in the catchment; and nine workers with prostate cancer diagnoses before entering the catchment. We censored PYAR for 1,345 workers who left the catchment before the study end date (and ignored 26 subsequent diagnoses). This analysis included 454 prostate cancer cases, whether first primary or not, among 9,905 workers contributing 193,960.3 PYAR. Prostate cancer incidence was lower than expected (SIR 0.88, 95%CI 0.80–0.97). Prostate cancer incidence did not vary by plant; was similar for short-term (<90 days of employment) and long-term workers; and did not vary with unlagged or 20-year lagged cumulative exposure (Supplemental File, Table SIII). Sensitivity analyses for defining the catchment, cases, and risk periods produced similar results (Supplemental File, Table SIV).

As of 12/31/2007, 338 prostate cancer cases were alive, five were lost to follow-up, 142 had died in the catchment, and 12 had died outside of the catchment. For the 142 deaths in the catchment, the death certificate specified prostate cancer as the underlying cause for 53 decedents and as a contributing cause for an additional 10 decedents. Consequently, death certificate ascertainment did not identify 56% (79 out of 142) of the prostate cancers identified by the state cancer registries among cohort members who had died in one of the registry states by 12/31/2007.

In internal analyses, directly standardized rates of prostate cancer incidence did not increase with unlagged or 20-year lagged categories of cumulative exposure (Supplemental File, Table SV). Similar results were observed when exposure lag periods of 10 and 30 years were considered and when short-term (<90 days employment) workers were excluded (data not shown). Risk of prostate cancer was not associated with cumulative PCB exposure in Cox regression models (Supplemental File, Table SVI).

**TABLE I.** Characteristics of Analyzed Workers, by Case Status, as of December 31, 2007

| Characteristic  | Female workers (n = 11,426)                      |                                     | Male workers (n = 9,891)                         |                                     |
|---|--|-------------------------------------|--|-------------------------------------|
|   | Other female workers                             |                                     | Other male workers                               |                                     |
|   | Cancer cases (n = 1,822)<br>No. (%) <sup>a</sup> | (n = 9,604)<br>No. (%) <sup>a</sup> | Cancer cases (n = 1,549)<br>No. (%) <sup>a</sup> | (n = 8,342)<br>No. (%) <sup>a</sup> |
| Plant   |  |                                     |  |                                     |
| Indiana   | 1138 (62)  | 6081 (63)                           | 588 (38)   | 2728 (33)                           |
| Massachusetts   | 580 (32)   | 2829 (30)                           | 633 (41)   | 3737 (45)                           |
| New York  | 104 (6)  | 595 (6)                             | 328 (21)   | 1877 (23)                           |
| Vital status as of December 31, 2007                  |  |                                     |  |                                     |
| Alive   | 724 (40)   | 7297 (76)                           | 638 (41)   | 6141 (74)                           |
| Dead  | 1087 (60)  | 2278 (24)                           | 904 (58)   | 2165 (26)                           |
| Lost  | 11 (<1)  | 29 (<1)                             | 7 (<1)   | 36 (<1)                             |
| Year of birth   |  |                                     |  |                                     |
| Median (range)  | 1930 (1896–1957)                                 | 1938 (1890–1959)                    | 1932 (1900–1958)                                 | 1942 (1888–1960)                    |
| Year of first employment                              |  |                                     |  |                                     |
| Median (range)  | 1957 (1939–1977)                                 | 1962 (1939–1977)                    | 1959 (1939–1977)                                 | 1965 (1939–1977)                    |
| Age at first employment                               |  |                                     |  |                                     |
| Median (range)  | 24.9 (15.2–58.3)                                 | 21.3 (14.0–64.9)                    | 24.5 (11.5–60.7)                                 | 22.1 (14.5–66.7)                    |
| Age at last employment                                |  |                                     |  |                                     |
| Median (range)  | 30.7 (16.0–68.2)                                 | 25.2 (15.9–69.7)                    | 29.5 (16.1–66.1)                                 | 24.6 (15.3–72.0)                    |
| Duration of employment (years)                        |  |                                     |  |                                     |
| <90 days  | 543 (30)   | 3190 (33)                           | 364 (23)   | 2273 (27)                           |
| 90 days – <1 year                                     | 347 (19)   | 2179 (23)                           | 345 (22)   | 2262 (27)                           |
| 1 year – <5 years                                     | 433 (24)   | 2318 (24)                           | 362 (23)   | 1950 (23)                           |
| 5 years – <10 years                                   | 182 (10)   | 794 (8)                             | 117 (8)  | 801 (10)                            |
| 10+ years   | 317 (17)   | 1123 (12)                           | 361 (23)   | 1056 (13)                           |
| Mean ± standard deviation                             | 4.7 ± 7.3  | 3.5 ± 6.1                           | 5.7 ± 8.1  | 3.7 ± 6.1                           |
| Median (range)  | 1.0 (0.0–35.1)                                   | 0.7 (0.0–35.0)                      | 1.3 (0.0–35.9)                                   | 0.8 (0.0–37.0)                      |
| Cumulative exposure to PCBs (unit-years) <sup>b</sup> |  |                                     |  |                                     |
| Unknown <sup>c</sup>                                  | 77 (4)   | 250 (3)                             | 27 (2)   | 76 (1)                              |
| Mean ± standard deviation                             | 850 ± 2100                                       | 630 ± 1700                          | 1000 ± 2300                                      | 640 ± 1600                          |
| Median (range)  | 100 (0.1–22000)                                  | 73 (0.0–26000)                      | 160 (0.3–21000)                                  | 110 (0.0–23000)                     |

<sup>a</sup>Result given as n (%), unless otherwise specified. Percentages may not sum to 100 due to rounding.<sup>b</sup>PCBs, polychlorinated biphenyls.<sup>c</sup>Cumulative exposure was unknown if workers had any time in a job with unknown exposure.

The incident cancer diagnoses are described in Table III by their status as aggressive or indolent. Median estimated cumulative PCB exposure is summarized for aggressive and indolent cancer diagnoses in Table IV for 11 major categories and some minor categories of special interest (stomach, uterine, and brain cancer because of previously observed elevated mortality [Ruder et al., 2014]). Among prostate cancer cases with known exposure and known status, the median cumulative exposures for aggressive cancer cases was significantly higher compared to localized

and regional cases. The median was higher, but not significantly, for respiratory cancers.

## DISCUSSION

Cancer is a major public health problem in the United States with annual incidence of 460.4/100,000 (1.67 million diagnoses estimated for 2014) and annual mortality of 174.8/100,000 (585,720 deaths estimated for 2014)

**TABLE II.** First Primary Cancer Standardized Incidence Ratios, by Gender and Overall<sup>a</sup>

| First primary cancer <sup>b</sup>           | Males (n = 9,891) |      |           | Females (n = 11,426) |      |           | Overall (n = 21,317) |      |           |
|---|-------------------|------|-----------|----------------------|------|-----------|----------------------|------|-----------|
|   | OBS               | SIR  | 95%CI     | OBS                  | SIR  | 95%CI     | OBS                  | SIR  | 95%CI     |
| All cancers combined                        | 1549              | 0.92 | 0.87–0.96 | 1822                 | 0.94 | 0.90–0.98 | 3371                 | 0.93 | 0.90–0.96 |
| MN of buccal and pharynx                    | 39                | 0.70 | 0.50–0.96 | 25                   | 0.80 | 0.52–1.19 | 64                   | 0.74 | 0.57–0.94 |
| MN of colon and rectum                      | 157               | 0.88 | 0.74–1.02 | 225                  | 1.08 | 0.94–1.23 | 382                  | 0.98 | 0.89–1.09 |
| MN of other digestive organs and peritoneum | 135               | 1.00 | 0.84–1.19 | 111                  | 0.89 | 0.73–1.07 | 246                  | 0.95 | 0.83–1.08 |
| MN of stomach                               | 40                | 1.23 | 0.88–1.68 | 18                   | 0.79 | 0.47–1.25 | 58                   | 1.05 | 0.80–1.36 |
| MN of respiratory and intrathoracic organs  | 344               | 1.16 | 1.04–1.29 | 354                  | 1.31 | 1.18–1.45 | 698                  | 1.23 | 1.14–1.33 |
| MN of breast                                | 6                 | 1.81 | 0.66–3.93 | 500                  | 0.80 | 0.73–0.87 | 506                  | 0.80 | 0.73–0.88 |
| MN of female genital organs                 | 0                 |      |           | 235                  | 0.90 | 0.79–1.02 | 235                  | 0.90 | 0.79–1.02 |
| MN of the uterus                            | 0                 |      |           | 105                  | 0.77 | 0.63–0.93 | 105                  | 0.77 | 0.63–0.93 |
| MN of the ovary                             | 0                 |      |           | 70                   | 0.93 | 0.72–1.17 | 70                   | 0.93 | 0.72–1.17 |
| MN of male genital organs                   | 436               | 0.82 | 0.75–0.90 | 0                    |      |           | 436                  | 0.82 | 0.75–0.90 |
| MN of prostate                              | 432               | 0.83 | 0.76–0.92 | 0                    |      |           | 432                  | 0.83 | 0.76–0.92 |
| MN of urinary organs                        | 153               | 0.94 | 0.80–1.11 | 106                  | 1.27 | 1.01–1.53 | 259                  | 1.05 | 0.93–1.19 |
| MN of thyroid and other endocrine organs    | 7                 | 0.56 | 0.22–1.15 | 14                   | 0.43 | 0.23–0.72 | 21                   | 0.46 | 0.29–0.71 |
| MN of other solid cancers                   | 96                | 0.76 | 0.62–0.93 | 68                   | 0.70 | 0.54–0.88 | 164                  | 0.73 | 0.62–0.85 |
| MN of the brain                             | 20                | 0.82 | 0.50–1.26 | 19                   | 0.80 | 0.48–1.25 | 39                   | 0.81 | 0.58–1.11 |
| MN of lymphatic and hematopoietic organs    | 131               | 0.88 | 0.73–1.04 | 139                  | 0.93 | 0.78–1.09 | 270                  | 0.90 | 0.80–1.01 |
| Ill-specified and residual                  | 45                | 1.11 | 0.81–1.49 | 45                   | 0.89 | 0.65–1.19 | 90                   | 0.99 | 0.80–1.22 |

MN, malignant neoplasm; OBS, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.

<sup>a</sup>The analysis included cases of first primary incident cancers identified using the nine state cancer registries (Connecticut, New York, Massachusetts, Rhode Island, Indiana, California, Texas, Florida, and North Carolina); split any gaps in the residence history at the midpoint and assigned the first half of the gap to the earlier state and the second half of the gap to the later state; and limited person-time at risk to the initial risk period (i.e., person-time at risk was censored at the date the worker was first known to be living outside the catchment).

<sup>b</sup>Results for all major cancer sites and selected minor cancer sites. Specific ICD-O-3 codes associated with each grouping are listed in Supplemental File, Table SII.

[Howlader et al., 2014]. In the United States, prostate cancer accounts for more male cancer diagnoses than lung cancer and, despite the high survival rate, is a leading cause of death [Brawley, 2012]. The known risk factors for prostate cancer are advanced age, family history, African-American race [Brawley, 2012], and higher latitude of residence [St-Hilaire et al., 2010]. While there are no well-established occupational or environmental risk factors, exposures to PCBs [Charles et al., 2003; Ruder et al., 2014] and pesticides [Ejaz et al., 2004; Mullins and Loeb, 2012] have been proposed. For several sites, including prostate cancer, our mortality update showed significant exposure–response relationships [Ruder et al., 2014]. For cancers with high survivability, incidence may be a better metric than mortality. Indeed, in our study, death certificates missed more than half of the prostate cancer diagnoses. Consequently, we analyzed incident cancers, to determine whether cancer groupings for which we had found excess mortality would also have elevated cancer incidence.

We expected to find elevated prostate cancer incidence in this cohort of PCB exposed workers because of the previously observed positive exposure–response relation with cumulative PCB exposure and prostate cancer

mortality; however, prostate cancer incidence was significantly reduced in the cohort compared to the SEER population. Furthermore, elevations were not observed for other incident cancers with the exception of respiratory cancers and, among women, urinary organ cancers. We considered several possible explanations for this apparent discrepancy.

First, our study could not benefit from a national cancer registry, as one does not exist [Buchanich et al., 2009]. We identified cases using cancer registries for nine states where 86% of deceased eligible workers had died through 2007. Cancer diagnoses outside of the catchment area or before the registries were operating were not available. Consequently, person-time for individuals outside the catchment was excluded when estimating expected numbers of cases. This calculation, however, relied on available residential histories, and the state of residence had to be assumed for 43% of the potential PYAR. Overestimation of the amount of time spent in the catchment would result in underestimated SIRs.

Second, our analyses used SEER rates, which are intended to be representative of the entire country. However, the SEER catchment comprises only 28% of the U.S. population [NCI, 2014]. If SEER rates actually

**TABLE III.** Cancer Diagnoses by Type

| First primary cancer                        | Aggressive <sup>a</sup> | In situ | Localized | Regional | Unknown | Total |
|---|-------------------------|---------|-----------|----------|---------|-------|
| All cancers combined                        | 1,509                   | 59      | 1,040     | 371      | 392     | 3,371 |
| MN of buccal and pharynx                    | 21                      | 0       | 15        | 27       | 1       | 64    |
| MN of colon and rectum                      | 145                     | 0       | 90        | 108      | 39      | 382   |
| MN of other digestive organs and peritoneum | 186                     | 0       | 27        | 17       | 16      | 246   |
| MN of the stomach                           | 36                      | 0       | 10        | 7        | 5       | 58    |
| MN of respiratory and intrathoracic organs  | 526                     | 0       | 87        | 46       | 39      | 698   |
| MN of breast                                | 125                     | 0       | 241       | 70       | 70      | 506   |
| MN of female genital organs                 | 101                     | 1       | 83        | 17       | 33      | 235   |
| MN of the uterus                            | 27                      | 1       | 48        | 6        | 23      | 105   |
| MN of the ovaries                           | 52                      | 0       | 12        | 4        | 2       | 70    |
| MN of male genital organs                   | 52                      | 0       | 303       | 36       | 45      | 436   |
| MN of the prostate                          | 51                      | 0       | 301       | 36       | 44      | 432   |
| MN of urinary organs                        | 60                      | 58      | 101       | 16       | 24      | 259   |
| Female                                      | 30                      | 19      | 40        | 7        | 10      | 106   |
| Male  | 30                      | 39      | 61        | 9        | 14      | 153   |
| MN of thyroid and other endocrine organs    | 2                       | 0       | 13        | 2        | 4       | 21    |
| MN of other solid cancers                   | 66                      | 0       | 56        | 13       | 29      | 164   |
| MN of the brain                             | 26                      | 0       | 5         | 1        | 7       | 39    |
| MN of lymphatic and hematopoietic organs    | 220                     | 0       | 20        | 17       | 13      | 270   |
| Multiple myeloma                            | 40                      | 0       | 0         | 0        | 0       | 40    |
| III-specified and residual                  | 5                       | 0       | 4         | 2        | 79      | 90    |

MN, malignant neoplasm.

<sup>a</sup>Aggressive is defined as distant stage at diagnosis or underlying cause of death due to same cause as cancer diagnosis.

overestimate national incidence, then SIRs would be underestimated. Ideally, a comparison of mean prostate cancer incidence rates inside and outside the SEER catchment could test this hypothesis for prostate cancer but rates for individual states outside the SEER catchment are unfortunately only available for more recent years and not for all of the years considered in our study. However, an examination of state-specific prostate cancer incidence rates for recent years [US Department of Health and Human Services et al., 2014] showed that Indiana incidence (but not Massachusetts or New York) was consistently below SEER incidence, so use of the SEER rates may have underestimated the prostate cancer SIR.

Third, our cohort is an older cohort and it is possible that members of our cohort were diagnosed, and subsequently died, before registries began collecting cases. Median birth year was 1930 (range 1896–1957) for women diagnosed with cancer and 1932 (range 1900–1958) for men diagnosed with cancer; median birth year was 1938 (range 1890–1959) for cancer-free women and 1942 (range 1888–1960) for cancer-free men (Table I). Since most cancer registries began ascertaining cases in 1976–1999, information about nonfatal cancer diagnoses among the 1,306 workers who died before 1976 or the 656 workers lost to follow-up (8% of the cohort) would not have been ascertained by us and these individuals would not have been included in our analysis.

Fourth, race was unknown, and White race assumed, for over half the cohort [Ruder et al., 2014]. Thus, it is possible that rates applied were too high or too low for a subset of the cohort. For example, because prostate cancer incidence rates are higher for African-American men [Brawley, 2012], if African-American rates were more appropriate for some of the men with unknown race, use of the higher rates would have resulted in increased expected incidence, but this would have resulted in an even lower prostate cancer SIR.

Fifth, for the external analyses, we used two prostate cancer incidence rate files for the SEER referent population [Howlader et al., 2014]. The first rate file (i) excluded second and later diagnosed cases from the numerator and (ii) excluded prevalent cases from the denominator and produced an SIR of 0.83 (Table II); the second rate file, which was only used for prostate cancer, (i) did not exclude second and later diagnosed cases from the numerator (although this is not likely to be a major issue for prostate cancer) and (ii) did not exclude prevalent cases from the denominator (a potentially major issue given the high prevalence of prostate cancer in the United States) and produced an SIR of 0.88 (Supplemental File, Tables SIII–SV). Merrill et al. [2012] estimated corrected prostate cancer incidence rates to be 9.9–13.7% higher than rates that did not include these adjustments. Larger differences were observed at older ages, with corrected rates for

**TABLE IV.** Estimated Median Cumulative PCB Exposure Levels (Unit-Years) for Aggressive Versus Non-Aggressive (Localized or Regional) Diagnoses<sup>a</sup>

| First primary cancer                        | Localized/Regional |                  | Aggressive <sup>b</sup> |        | P-value <sup>c</sup> |
|---|--------------------|------------------|-------------------------|--------|----------------------|
|   | No.                | Median           | No.                     | Median |                      |
| MN of buccal and pharynx                    | 40                 | 120 <sup>d</sup> | 20                      | 100    | 0.94                 |
| MN of colon and rectum                      | 191                | 150              | 140                     | 140    | 0.86                 |
| MN of other digestive organs and peritoneum | 43                 | 390              | 179                     | 160    | 0.080                |
| MN of the stomach                           | 17                 | 410              | 33                      | 510    | 0.98                 |
| MN of respiratory and intrathoracic organs  | 133                | 70               | 517                     | 120    | 0.074                |
| MN of breast                                | 302                | 96               | 119                     | 87     | 0.96                 |
| MN of female genital organs                 | 97                 | 61               | 94                      | 100    | 0.48                 |
| MN of the uterus                            | 52                 | 73               | 25                      | 110    | 0.25                 |
| MN of the ovary                             | 15                 | 120              | 48                      | 120    | 0.77                 |
| MN of male genital organs                   | 336                | 150              | 51                      | 700    | <0.0001              |
| MN of prostate                              | 334                | 150              | 50                      | 630    | <0.0001              |
| MN of urinary organs                        | 115                | 170              | 59                      | 310    | 0.89                 |
| Female                                      | 46                 | 70               | 30                      | 190    | 0.28                 |
| Male  | 69                 | 350              | 29                      | 320    | 0.74                 |
| MN of thyroid and other endocrine organs    | 15                 | 160              | 2                       | 3000   | 0.11                 |
| MN of other solid cancers                   | 67                 | 59               | 64                      | 78     | 0.44                 |
| MN of the brain                             | 6                  | 31               | 25                      | 110    | 0.15                 |
| MN of lymphatic and hematopoietic organs    | 37                 | 110              | 211                     | 120    | 0.68                 |

MN, malignant neoplasm.

<sup>a</sup>Limited to diagnoses for workers with no time in an unknown job category.

<sup>b</sup>Aggressive is defined as distant stage at diagnosis or underlying cause of death due to same cause as cancer diagnosis.

<sup>c</sup>Significance test for median based on Wilcoxon two-sample test.

<sup>d</sup>Cumulative exposure (in unit-years) is product of the number of days in each department and job-title and the assigned score, summed over all jobs worked, and divided by 365.25.

White males 80 years or older estimated to be 20% higher than uncorrected rates [Merrill and Sloan, 2012]. Thus, in the second analysis it is possible that we underestimated the expected number of prostate cancer cases and consequently overestimated the prostate cancer SIRs, but this does not explain the observed deficit or the lack of association with estimated exposure to PCBs.

Finally, recommendations for screening using prostate-specific antigen (PSA) testing in the late 1980s had an enormous impact on the numbers of diagnoses in subsequent years [Leach and Thompson, 2012], but adherence to screening guidelines can vary. For example, screening for working Americans with no cancer history (based on National Health Interview Survey data) varied by job status with 53% and 61% of blue- and white-collar men screened in 1999, respectively, and declining to 37% and 50% by 2010 [Clarke et al., 2012]. If the men in our cohort were less likely than other men to be screened, prostate cancer diagnoses would have been under ascertained in our cohort, leading to underestimated prostate cancer SIRs.

We did not observe positive associations between prostate cancer incidence and estimated cumulative PCB exposure in this cohort of PCB exposed workers. Both

duration of employment and estimated PCB exposure in our cohort decreased with decade of first exposure (data not shown) so differential PSA screening rates by year could obscure an exposure–response association. In a post hoc analysis, we observed significantly higher median estimated cumulative PCB exposure for workers with aggressive prostate cancer diagnoses (median 700 unit-years) compared to regional/localized diagnoses (median 150 unit-years) (Table IV;  $P < 0.0001$ ). Since prostate cancer aggressiveness may be determined when the tumor is initially formed [Giovannucci et al., 2007; Penney et al., 2013], it is possible that higher exposed workers developed aggressive tumors differentially at a higher rate compared to lower exposed workers. However, given the number of prostate risk factors and the role genetic susceptibility plays, it is difficult to interpret the difference in PCB exposure we observed [Boyd et al., 2012].

There are limited and conflicting data on the relationship between PCBs and prostate cancer. In a serum concentration study Koutros et al. [2015] found no association between total PCBs and individual PCB congeners and metastatic prostate cancer except for PCB congener 44 which was inversely associated with risk. Sawada et al. [2010] found an

inverse risk of total PCBs in plasma and advanced prostate cancer. Since the workers in our cohort were exposed to PCB mixtures which contained estrogenic, nonestrogenic, and antiandrogenic PCB congeners [Connor et al., 1997; Wolff et al., 1997; Hopf et al., 2009], etiologic mechanisms are likely complicated.

Based on the known association of PCBs with endocrine disruption [Bonefeld-Jorgensen et al., 2014; Annamalai and Namasivayam, 2015], we expected to observe similar aggressive versus indolent results for other cancers associated with hormone effects (i.e., breast, uterine, ovarian, and thyroid cancers) [Buranatrevedh and Roy, 2001; Duntas, 2015]. However, we did not observe higher median cumulative PCB exposures for aggressive breast, uterine, and ovarian cancers. For thyroid cancer, the median cumulative PCB exposure for aggressive cancers was an order of magnitude higher compared to local/regional cancers but there were only two aggressive thyroid cancers. While suggestive of an association, this should be explored in a larger study.

Our mortality paper [Ruder et al., 2014] did not focus on lung cancer because it was not an *a priori* outcome and we did not have smoking data on cohort members. Smoking is the most important risk factor for lung cancer [Recio-Vega et al., 2013]. While lung cancer mortality was (borderline) elevated in the full cohort (766 deaths, SMR 1.07, 95%CI, 0.99–1.15), the elevation disappeared when we removed the short-term (<90 days) workers (short-term SMR 1.34, long-term SMR 0.99). Several papers have associated serum PCB levels with elevated lung cancer rates in non-occupational studies, whether not adjusting [Onozuka et al., 2009; Li et al., 2015] or adjusting [Recio-Vega et al., 2013] for smoking status. The present cancer incidence study also found elevated respiratory cancer in a PCB cohort but additional studies with both occupational exposure and smoking data would be needed to confirm the association.

Our study has several significant strengths. It is the largest cohort of former capacitor workers exposed to PCBs and includes a detailed exposure assessment. The data available to construct job-exposure matrices included individual work histories, detailed job descriptions, and exposure measurements collected at the plants [Hopf et al., 2009, 2010, 2014]. However, as in other records-based studies, we had no information on family history or genetic susceptibility; lifestyle choices that could affect mortality (such as obesity); or previous or subsequent employment.

In conclusion, previously observed associations with cumulative PCB exposure and prostate cancer mortality were not confirmed in this analysis; however, prostate cancer stage may explain the apparent discrepancy. Our results may contribute to the decision-making process for determining which men could benefit from PSA testing. Men with aggressive prostate cancer had significantly higher levels of estimated cumulative PCB exposure than those with

nonaggressive cancer. If it follows that incidence of aggressive prostate cancer is higher among men with high cumulative PCB exposure, then men who have been exposed to high levels of PCBs might benefit from PSA testing even more than men in the general population.

## DATA USE DISCLAIMERS

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This study was approved by the Connecticut DPH HIC. Certain data used in this publication were obtained from DPH. The authors assume full responsibility for analyses and interpretation of these data.

The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (FCDS) under contract with the Florida Department of Health (FDOH). The views expressed herein are solely those of the author(s) and do not necessarily reflect those of the FCDS or FDOH.

Cancer incidence data used in this study were obtained from the New York State Cancer Registry.

Cancer incidence data have been provided by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, 1100W. 49th Street, Austin, Texas, 78756, <http://www.dshs.state.tx.us/tcr/default.shtm>, or (512) 458-7523.

Cancer incidence data used in this study were also obtained from cancer registries in Indiana, Massachusetts, North Carolina, and Rhode Island.

## AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the conception, analysis, writing, and revision of the work, and all agree to be accountable for all aspects of the work.



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## ETHICAL APPROVAL AND INFORMED CONSENT

This study (HSRB-08-DSHEFS-02) was approved by the NIOSH Human Subjects Review Board and participating state cancer registries. As a records study, it was exempted from informed consent requirements.

## DISCLOSURE (AUTHORS)

The authors report no conflicts of interest.

## DISCLOSURE BY AJIM EDITOR OF RECORD

Rodney Ehrlich declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

## DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. The use of trade names is for identification only and does not imply endorsement by the US Department of Health and Human Services or by the Centers for Disease Control and Prevention.

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