Title: Cancer incidence among capacitor manufacturing workers exposed to polychlorinated biphenyls.

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ABSTRACT

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 compared between aggressive (fatal/distant stage) and localized/regional cancers.

Results: We identified 3371 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.

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 1938-1977 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 (≥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 (≥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 National Institute for Occupational Safety and Health (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 members had moved. We focused on prostate cancer, based on our mortality study results and its high survivability (~100% five-year survival and 99% ten-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 one 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, 7006 (31%) of the eligible workers had died with 6055 (86%) of these deaths occurring in the registry states (**Supplemental File, Table S1**).

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 S2**). 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. [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 1973-1975. 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. 2014; Hopf, et al. 2009; Hopf, et al. 2010]. 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 unit-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 [Howlader, 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**) for details). 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 that aggressive prostate cancers were fatal (underlying cause prostate cancer) or distant stage at diagnosis [Koutros, et al. 2013]. 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 4084 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; 1507 workers (53 diagnoses) with no time in the catchment; and 46 workers diagnosed before entering the catchment. We censored PYAR for 2244 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 1**. For the analysis of first primary invasive cancer, 3371 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 2). 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 S3**). Sensitivity analyses for defining the catchment, cases, and risk periods produced similar results (**Supplemental File, Table S4**).

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 S5**). 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 S6**).

The incident cancer diagnoses are described in **Table 3** by their status as aggressive or indolent. Median estimated cumulative PCB exposure is summarized for aggressive and indolent cancer diagnoses in **Table 4** 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) [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 [National Cancer Institute 2015]. If SEER rates actually 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 [Centers for Disease Control and Prevention and National Cancer Institute 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 1). Since most cancer registries began ascertaining cases in 1976-1999, information about nonfatal cancer diagnoses among the 1306 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 (a) excluded second and later diagnosed cases from the numerator and (b) excluded prevalent cases from the denominator and produced an SIR of 0.83 (**Table 2**); the second rate file, which was only used for prostate cancer, (a) 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 (b) 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 S3-S5**). Merrill and colleagues estimated corrected prostate cancer incidence rates to be 9.9-13.7% higher than rates that did not include these adjustments [Merrill, et al. 2012]. Larger differences were observed at older ages, with corrected rates for 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 4; $p<0.0001$). Since prostate cancer aggressiveness may be determined when the tumor is initially formed (Giovannucci et al 2006; 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 [Annamalai and Namasivayam 2015; Bonefeld-Jorgensen, et al. 2014], 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 [Li, et al. 2015; Onozuka, et al. 2009] 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. 2014; Hopf, et al. 2009; Hopf, et al. 2010]. 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

The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

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, 1100 W. 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.

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Table 1: Characteristics of analyzed workers, by case status, as of 31 December 2007

Characteristic	Female workers (n=11,426)		Male workers (n=9,891)	
	Cancer cases (n=1,822) No. (%) [1]	Other female workers (n=9,604) No. (%) [1]	Cancer cases (n=1,549) No. (%) [1]	Other male workers (n=8,342) No. (%) [1]
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 31 December 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.-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) [2]				
Unknown [3]	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)

[1] Result given as n (%), unless otherwise specified. Percentages may not sum to 100 due to rounding.

[2] PCBs: polychlorinated biphenyls

[3] Cumulative exposure was unknown if workers had any time in a job with unknown exposure.

Table 2: First primary cancer standardized incidence ratios, by gender and overall [1]

	Males (n=9,891)			Females (n=11,426)			Overall (n=21,317)		
First primary cancer [2]	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

[1] 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).

[2] 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 S2**.

Table 3: Cancer diagnoses by type

First primary cancer	Aggressive [1]	In Situ	Localized	Regional	Unknown	Total
All cancers combined	1509	59	1040	371	392	3371
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						
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
Ill-specified and residual	5	0	4	2	79	90

MN – malignant neoplasm

[1] Aggressive is defined as distant stage at diagnosis or underlying cause of death due to same cause as cancer diagnosis.

Table 4: Estimated median cumulative PCB exposure levels (unit-years) for aggressive versus non-aggressive (localized or regional) diagnoses [1]

	Localized/Regional		Aggressive [2]		
First primary cancer	No.	Median	No.	Median	P-value [3]
MN of buccal and pharynx	40	120	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

1 Limited to diagnoses for workers with no time in an unknown job category.
2 Aggressive is defined as distant stage at diagnosis or underlying cause of death due to same cause as cancer diagnosis.
3 Significance test for median based on Wilcoxon two-sample test.
4 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.

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SUPPLEMENTAL FILE

Additional details on state of residence

Multiple sources of address information were considered. Workers were assumed to have resided in the states where the plants were located while employed. Some addresses during the period of employment (starting as early as 1939 when the Massachusetts plant opened) were available from plant personnel records. Various tracing efforts from previous studies of this cohort [Prince, et al. 2006; Ruder, et al. 2006; Silver, et al. 2009] included the Internal Revenue Service, Post Office, and credit services. Together, these sources provided address information for 22,249 eligible workers (97%). Finally, eligible workers were also matched to LexisNexis® (a private vendor of residential information) in 2011 using first and last name, last known address, date of birth and Social Security Number (SSN); this provided additional address information for 19,235 eligible workers (84%).

Since only changes in the state of residence were relevant, these sources of address information were combined to create a residence history for each worker. State of residence was estimated for time periods with no known address information by dividing the gap at the midpoint and assigning the earlier state to the first half of the gap and the later state to the second half. For a given follow-up year, the worker was considered to be in the registry catchment if known to be living in at least one state associated with the catchment in that year.

SIR sensitivity analyses for prostate cancer

The primary analysis used data from the nine cancer registries to identify cases and the corresponding states to define the catchment. To evaluate the decision to expand the cancer

registries beyond the states where the plants were located, life-table analyses were repeated using just the cancer registries for the three study states (and defining the catchment to be New York 1976-1981; New York and Massachusetts 1982-1986; and New York, Massachusetts, and Indiana 1987-2007).

Because state cancer registries generally will not release information about tumors only known to them through other state registries, we evaluated the potential under-ascertainment of incident cases by repeating life-table analyses additionally including prostate cancer deaths identified from our earlier mortality study that occurred in any of the nine cancer registry states [Ruder, et al. 2014] that may not have been included as cases in the primary analysis. For these, we estimated an approximate diagnosis date as seven years prior to the death date [Antonarakis, et al. 2007] and required the estimated diagnosis date to be in the catchment.

The primary analysis was limited to person-time in the first (initial) risk period; however, since others have considered disjoint risk periods when estimating SIRs [Bender, et al. 2007] we performed additional life-table analyses that considered all person-time while residing in the catchment.

In the absence of complete residential histories, Bender et al. [Bender, et al. 2006] recommended conducting uncertainty analyses to understand the limitations of the available residential history information. Our primary analysis assigned states of residence to gaps in the residential history by splitting the gap at the midpoint. To evaluate this decision, we repeated the life-table analyses

assigning the entire gap to the earlier state. Next we repeated the life-table analyses assigning the entire gap to the later state.

Since the date last observed was updated based on cancer registry information for nine workers previously thought to be dead (n=1) or lost to follow-up (n=8) we repeated the life-table analyses excluding these workers because other workers lost to follow-up not known to have been diagnosed with cancer were not similarly brought forward.

External analyses for prostate cancer

Plant-specific prostate cancer SIRs were compared using Poisson regression models (SAS 9.2 GENMOD procedure, SAS Institute Inc., Cary, NC): the dependent variable was the number of cases (assumed to follow a Poisson distribution); the independent variables included plant indicator variables, and an offset term (with parameter fixed at 1.0) reflected the expected number of prostate cancer cases in each age and calendar-year stratum. Model parameters reflected the ratios of SIRs and can be interpreted as standardized rate ratios in the absence of a plant-age interaction [Armstrong 1995]. Similar methods were used to compare prostate cancer SIRs between short-term (<90 days of employment) and long-term workers.

Internal analyses for prostate cancer

Directly standardized prostate cancer incidence rates among workers with higher cumulative exposure were compared to rates among workers in the lowest cumulative exposure category. SRR 95% CIs were estimated using approximate methods [Rothman and Greenland 1998] and tests of linear trend for cumulative exposure using methods described by Rothman [Rothman

1986]. To account for potential latency, we considered exposure lag periods of 0, 10, 20, and 30 years.

Cox regression was used to estimate prostate cancer hazard ratios for workers with higher compared with lower cumulative exposure. In these analyses, age was specified as the time variable, cumulative exposure was time-dependent, and controls were matched to cases within risk sets on race and attained age. All eligible controls were included and the resulting matched risk sets were analyzed using conditional logistic regression (SAS 9.2 PHREG procedure, ibid.), equivalent to a Cox proportional hazards model stratified on race. Various transformations of cumulative exposure (continuous variable) were evaluated including square root, natural log, and restricted cubic splines. Categorical models used quintiles of the exposure distribution among cases. Confounding was evaluated for birth and calendar year. Exposure lag periods of 0 to 30 years were evaluated; the best-fitting lag period was selected based on model fit (AIC, Akaike's Information Criterion). Cutpoints partitioning exposure into three windows by levels of hormonal activity--exposure accrued before age 23, from age 23 to age 49, and at 50 years or older – were also considered [Agalliu, et al. 2005]. Effect modification was evaluated for plant using the likelihood ratio test for interaction. To evaluate the effect of changes in prostate cancer screening and guidelines in the late 1980s, we tested for interaction between cumulative exposure and calendar year. The proportional hazards assumption was evaluated by the likelihood ratio test for interaction between age and cumulative exposure.

We repeated internal analyses (SRRs and Cox regression) after excluding short-term workers because a large percentage of the cohort had worked fewer than 90 days [Ruder, et al. 2014].

SUPPLEMENTAL RESULTS

Cancer diagnoses and ascertainment

Diagnosis dates of included cancers were based on year only for 28 matches, month and year only for 2106 matches, and complete for 1946 matches. The cancer registries were unable to provide a diagnosis year for four matches; for these, a diagnosis date was imputed as the date of death minus the approximate duration with the disease, when available (n=2), or as the midpoint of the years for which the registry was in operation (n=2).

Matching the cohort to the cancer registries led to our extending date last observed for 23 workers previously thought to be lost to follow-up and two workers previously thought to be deceased. After excluding ineligible workers who had died (n=1306) or were otherwise lost to follow-up (n=656) before their respective cancer registry was in operation, 22,903 workers were eligible for the primary cancer incidence analysis (10,993 male workers were eligible for the prostate cancer analysis). Through 2007, 7006 (31%) of the eligible workers died and 6055 (86%) of these deaths occurred in one of the nine registry states (Indiana, 559; Massachusetts, 2735; New York, 1867; California, 166; Connecticut, 77; Florida, 463; North Carolina, 57; Rhode Island, 77; and Texas, 54); the remaining deaths occurred in other states, U.S territories, or the District of Columbia (n=872), or at unknown locations (n=79) (Supplemental Table S1).

Results of internal analyses for prostate cancer

In separate Cox regression models, both birth year and calendar year were confounders. Results were adjusted for calendar year since prostate cancer incidence increased dramatically starting in

the late 1980s when prostate-specific antigen screening began [Etzioni, et al. 1999], and continuing in 1992 when screening was recommended for asymptomatic men over 50 [American Cancer Society 2012]. Results (not shown) were similar when exposure lag periods of 10, 20, and 30 years were applied; results are presented based on a 20-year lag period which was best-fitting in an earlier analysis of prostate cancer mortality [Ruder, et al. 2014]. In simple models, prostate cancer incidence was not significantly associated with cumulative exposure (Supplemental Table S6, Models 1 and 3). Adjusting for calendar year improved model fit, but associations remained null (Supplemental Table S6, Models 2 and 4). Associations remained null (data not shown) for models that excluded short-term workers, that evaluated transformations of cumulative exposure (log, square root, and restricted cubic spline), and that evaluated exposure age windows. Plant and calendar year were evaluated and determined not to be effect modifiers. Including terms for time since last exposure did not improve model fit and the adjusted association remained null. The assumption of proportional hazards was not violated (data not shown).

Supplemental Table S1: Cancer registries, ascertainment, and cohort deaths among 22,903 PCB cohort members eligible for the cancer incidence study

State	PCB plant located here	Complete ascertainment from	Cohort deaths through 2007	
California	No	1988	166	2.4%
Connecticut	No	1973	77	1.1%
Indiana	Yes	1987	559	8.0%
Florida	No	1997	463	6.6%
Massachusetts	Yes	1982	2735	39.0%
New York	Yes	1976	1867	26.6%
North Carolina	No	1999	57	0.8%
Rhode Island	No	1986	77	1.1%
Texas	No	1995	54	0.8%
Total in registry states			6055	86.4%
Other states, territories, or District of Columbia	No		872	12.4%
Unknown	No		79	1.1%
Total			7006	100%

Supplemental Table S2: Recode from ICD-O-3 codes reported by cancer incidence registries to diagnostic minor codes used in the NIOSH Lifetable Analysis System (LTAS.NET) [1]

Major Category	Minor	Minor Category	ICD-10 Codes	ICD-O-3 Site Codes	ICD-O-3 Histology Codes
MN of buccal cavity and pharynx	1	MN of lip	C00	C000-C009	All excluding 9140, 9050-9055, and 9590-9989
	2	MN of tongue	C01, C02	C019-C029	
	3	MN of other buccal cavity	C03-C08	C039-C069, C079-C089	
	4	MN of pharynx	C09-C14	C090- C119, C129-C148	
MN of colon and rectum	5	MN of colon	C18	C180-C189	
	6	MN of rectum	C19, C20	C199, C209	
MN of other digestive organs and peritoneum	7	MN of esophagus	C15	C150- C159	
	8	MN of stomach	C16	C160-C169	
	9	MN of small intestine	C17	C170-C179	
	10	MN of biliary, liver, gall bladder	C22-C24	C220, C221, C239-C249	
	11	MN of pancreas	C25	C250-C259	
	12	MN of anus, peritoneum, other, and unspecified digestive	C21, C26, C48	C210-C212, C218, C260, C268, C269, C422, C480-C482, C488	
MN of respiratory and intrathoracic organs	13	MN of larynx	C32	C320-C329	
	14	MN of trachea, bronchus, and lung	C33, C34	C339-C349	
	15	MN of pleura	C38.4	C384	
	16	MN of other respiratory and intrathoracic organs	C30, C31, C37, C38.0-C38.3, C38.8, C39	C300,C301, C310-C319, C379, C380-C383, C388, C390,	

Major Category	Minor	Minor Category	ICD-10 Codes	ICD-O-3 Site Codes	ICD-O-3 Histology Codes
				C398, C399	
MN of breast	17	MN of breast	C50	C500-C509	
MN of female genital organs	18	MN of cervix uteri	C53	C530-C539	
	19	MN of other and unspecified parts of uterus	C54, C55, C58	C540-C549, C559, C589	
	20	MN of ovary, fallopian tube, and broad ligament	C56, 57.0-C57.4, C57.8	C569-C574, C578	
	21	MN of other and unspecified female genital organs	C51, C52, C57.7, C57.9	C510-C519, C529, C577, C579	
MN of male genital organs	22	MN of prostate	C61	C619	
	23	MN of testes	C62	C620-C629	
	24	MN of other and unspecified male genital organs	C60, C63	C600-C609, C630-C639	
MN of urinary organs	25	MN of kidney	C64-C66	C649, C659, C669	
	26	MN of bladder and other urinary organs	C67, C68, D09.0 [2]	C670-C689	
MN of thyroid and other endocrine glands	27	MN of thyroid gland	C73	C739	
	28	MN of other endocrine glands	C74, C75	C740-C749, C750-C759	
MN of other solid cancers	29	MN of bone	C40, C41	C400-C419	
	30	Malignant melanoma of skin	C43	C440-C449	8720-8790
	31	Kaposi sarcoma	C46	Not used	9140
	32	Mesothelioma	C45	Not used	9050-9055
	33	MN of connective	C49	C490-C499	All excluding 9140, 9050-9055, and 9590-

Major Category	Minor	Minor Category	ICD-10 Codes	ICD-O-3 Site Codes	ICD-O-3 Histology Codes
		tissue			9989
	34	MN brain and other parts of nervous system	C47, C70-C72	C470-C479, C700-C729	
	35	MN eye	C69	C690-C699	
Malignant neoplasms of lymphatic and hematopoietic tissue	36	Hodgkin lymphoma	C81	Not used	9650- 9667
	37	Non-Hodgkin lymphoma	C82-C85, C88.0, C88.3, C91.4, C96.0-C96.3, C96.7	Not used	9590, 9591, 9596, 9670, 9671, 9673, 9675, 9678- 9680, 9684, 9687, 9688, 9689-9691, 9695, 9698-9702, 9705, 9708, 9709, 9712, 9714-9719, 9724-9729, 9735, 9737, 9738, 9740, 9750, 9754-9759, 9761, 9764, 9940
	38	Multiple myeloma	C90	Not used	9731-9734
	39	Leukemia and aleukemia	C91.0-C91.3, C91.5, C91.7, C91.9, C92-C95	Not used	9742, 9800, 9801, 9805, 9820, 9823, 9826, 9827, 9831-9837, 9840, 9860, 9861, 9863, 9866, 9867, 9870-9876, 9891, 9895-9897, 9910, 9920, 9930, 9931, 9945, 9946, 9948, 9963
	40	Other lymphatic and hematopoietic neoplasms	C88.2, C88.7, C88.9, C96.9, D45, D46.1-D46.4, D46.7, D46.9, D47.1, D47.3, D47.7	Not used	9751, 9760, 9762, 9950, 9960-9962, 9970, 9975, 9980, 9982-9987, 9989
Ill-specified and residual	41	MN of Ill-specified and residual sites	C44, C76, C77, C80, C97	C440-C449	All excluding 8720-8790, 9140, 9050-9055, and 9590-9989
				C760-C768, C809, C420-C424, C770-C779	All excluding 9140, 9050-9055, and 9590-9989

Abbreviations: ICD-O-3, International Classification of Diseases for Oncology, 3rd Edition; ICD-10, International Classification of Diseases, 10th Revision; MN, malignancy; SEER, Surveillance, Epidemiology, and End Results Program

[1] Table adapted from supplemental table S5 in Daniels RD, Kubale TL, Yiin JH, Dahm MM, Hales TR, Baris D, Zahm SH, Beaumont JJ, Waters KM, Pinkerton LE. Mortality and cancer incidence in a pooled cohort of U.S. firefighters from San Francisco, Chicago and Philadelphia. Occupational and Environmental Medicine 2014;71:388-97.

[2] Urinary bladder incidence cases originally coded in situ (Behavior=2) were recoded to invasive (Behavior=3) per SEER protocol.

Supplemental Table S3: Prostate cancer standardized incidence ratios

Analysis [1]	No. workers [2]	PYAR	OBS	EXP	SIR	95% CI
All workers	9905	193,960.3	454	515.6	0.88	0.80-0.97
By plant						
Indiana	2208	37,631.0	99	123.1	0.80	0.65-0.98
Massachusetts	3319	64,341.4	167	180.6	0.92	0.79-1.08
New York	4378	91,987.8	188	211.9	0.89	0.77-1.02
By employment duration						
Short-term workers (< 90 days)	2638	51,462.5	96	108.9	0.88	0.71-1.08
Long-term workers (90+ days)	7267	142,497.8	358	406.7	0.88	0.79-0.98

Abbreviations: PYAR – person-years at risk, OBS – observed number of cases, EXP – expected number of cases based on SEER rates, SIR – standardized incidence ratio, CI – confidence interval

[1] The analysis included prostate cancer cases identified using the nine state cancer registries (CT, NY, MA, RI, IN, CA, TX, FL, and NC); 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).

[2] The number of workers (9905) and prostate cancer cases (454) differs slightly from those reported in table 2 (9891 and 432, respectively) because the prostate cancer analysis only excluded workers with a prostate cancer diagnosis before the cancer registry begin date whereas the analysis of first primary cancer excluded workers with any cancer diagnosis before the cancer registry begin date.

Supplemental Table S4: Prostate cancer standardized incidence ratios for the sensitivity analyses

Sensitivity analyses	No. workers	PYAR	OBS	EXP	SIR	95% CI
S1: Included only cases from the IN, MA, and NY cancer registries [1]	9134	181,478.6	396	464.3	0.85	0.77-0.94
S2: Included (a) all cancer-registry identified cases (primary) and (b) death-certificate identified cases who resided in any of the nine registry states [2]	9899	193,902.5	465	515.1	0.90	0.82-0.99
S3: Included all risk periods [3]	9898	200,632.2	473	541.7	0.87	0.80-0.96
S4: Assigned entire gap to earlier state [4]	10549	215,287.0	454	531.2	0.85	0.78-0.94
S5: Assigned entire gap to later state [5]	9492	194,584.6	470	535.5	0.88	0.80-0.96
S6: Excluded "lost and found" workers [6]	9896	193,821.6	451	515.1	0.88	0.80-0.96

Abbreviations: PYAR – person-years at risk, OBS – observed number of cases, EXP – expected number of cases based on SEER rates, SIR – standardized incidence ratio, CI – confidence interval

The primary analysis included cases identified using the nine state cancer registries (CT, NY, MA, RI, IN, CA, TX, FL, and NC); 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).

[1] S1 was like the primary analysis except that it defined the catchment to be the states where the plants were located (NY, MA, and IN) and limited cases to those identified using the cancer registries affiliated with these three states.

[2] S2 was like the primary analysis except that it additionally included cases from the nine registry states who were identified using death certificates.

[3] S3 was like the primary analysis except that all risk periods were included (i.e., all person-time at risk in the catchment contributed to the denominator).

[4] S4 was like the primary analysis except that gaps in the residence history were assigned to the earlier state.

[5] S5 was like the primary analysis except that gaps in the residence history were assigned to the later state.

[6] S6 was like the primary analysis except that nine "lost and found" workers were excluded.\

Supplemental Table S5: Observed and expected numbers of incident prostate cancers, standardized incidence ratios, and directly standardized rate ratios, by exposure category [1]

Cumulative exposure category (unit-years) [2]	PYAR	OBS	EXP	SIR	95% CI	SRR	95% CI
Unlagged							
1: <23	42,320.7	90	102.5	0.88	0.71-1.08	1	(referent)
2: 23-<99	42,019.1	90	100.1	0.90	0.72-1.11	1.06	0.78-1.42
3: 99-<330	42,457.4	90	104.9	0.86	0.69-1.05	1.03	0.76-1.38
4: 330-<1100	35,085.5	89	90.7	0.98	0.79-1.21	1.16	0.86-1.56
5: 1100+	30,220.4	88	108.8	0.81	0.65-0.997	1.00	0.73-1.38
							p_{trend}=0.99
20 year lag							
1: <23	74,696.8	90	107.9	0.83	0.67-1.02	1	(referent)
2: 23-<86	30,924.1	91	89.9	1.01	0.82-1.24	1.25	0.93-1.68
3: 86-<320	36,098.5	90	111.6	0.81	0.65-0.99	1.02	0.76-1.37
4: 320-<1100	27,792.0	89	92.0	0.97	0.78-1.19	1.18	0.88-1.58
5: 1100+	22,591.9	87	105.6	0.82	0.66-1.02	1.07	0.78-1.47
							p_{trend}=0.90

Abbreviations: PYAR – person-years at risk, OBS – observed number of cases, EXP – expected number of cases based on SEER rates, SIR – standardized incidence ratio, CI – confidence interval, SRR – standardized rate ratio, p_{trend} – p-value for linear trend test

[1] Results exclude seven cases and 1857 PYAR with unknown cumulative exposure.
[2] Categories of cumulative exposure based on the quintiles of the lag-specific case distribution.

Supplemental Table S6: Cox regression models for prostate cancer incidence with estimated cumulative exposure (lagged by 20 years) [1]

	Model 1		Model 2		Model 3		Model 4	
Model term	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Cumulative exposure								
At 1000 unit-years	0.965	0.913-1.013	0.980	0.929-1.028				
Category (unit-years)								
1: <23					1	(reference)	1	(reference)
2: 23-<86					1.23	0.92-1.65	1.20	0.90-1.62
3: 86-<320					1.00	0.74-1.33	1.00	0.74-1.34
4: 320-<1100					1.16	0.86-1.56	1.14	0.85-1.54
5: 1100+					0.95	0.70-1.27	1.04	0.77-1.40
Calendar year								
<1990			1	(reference)			1	(reference)
1990-1994			2.73	1.79-4.26			2.71	1.77-4.23
1995-1999			3.42	2.32-5.21			3.41	2.31-5.20
2000+			3.42	2.38-5.12			3.43	2.38-5.12
Likelihood ratio test for exposure								
Degrees of freedom	1		1		4		4	
Chi-square	1.98		0.62		4.40		2.56	
P-value	0.16		0.43		0.35		0.63	
Model fit								
-2 log likelihood	7036.58		6977.98		7034.16		6796.04	
Akaike's information criterion	7038.58		6985.98		7042.16		6990.04	

Abbreviations: HR – hazard ratio, CI – profile likelihood based confidence interval

[1] For all models, controls were matched to cases within risk sets on race in addition to attained age and all eligible controls were included. Cumulative exposure (lagged by 20 years) was evaluated within risk sets at the case's failure age and treated as a continuous variable in models 1 and 2 and as a categorical variable in models 3 and 4. The effect of cumulative exposure is adjusted for age at diagnosis in models 1 and 3 and for age at diagnosis and calendar year in models 2 and 4.

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