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Mortality and cancer incidence in a large cohort of lead-exposed workers

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Abstract

Introduction: **Inorganic lead is a common occupational exposure and a probable carcinogen (International Agency for Research on Cancer, group 2A). Here, we analyse mortality and cancer incidence in a large cohort of US workers with measured blood lead levels.**

Methods: **We updated the mortality follow-up for a cohort of 58 000 male lead-exposed workers and followed a subset of 36 000 for cancer incidence, both through 2021. The highest recorded blood lead was used as the exposure metric in internal exposure–response analyses via Cox regression. Time at risk began at the first blood lead test.**

Results: **The median birth year was 1959 and the average year of the first blood test was 1998. The mean highest blood lead was 26 μg/dL. There were 8832 deaths. The mortality results showed strong positive associations between blood lead and lung cancer, pancreatic cancer, heart disease, chronic obstructive pulmonary disease, and chronic renal disease. There were 6125 incident cancers. The lung cancer incidence showed a marked positive trend with higher lead levels; the liver cancer incidence also had a significant positive trend. Thyroid and prostate cancer showed marked negative trends.**

Conclusion: **High blood lead levels were associated with several causes of mortality and cancer incidence, most markedly lung cancer. While lung cancer trends might be related to smoking, there is no a priori reason why workers with higher blood lead would have smoked more and, in a subset of 200 workers with smoking data, there was no such evidence. The lung cancer rate ratios in the order of 2.0–2.5 are also very unlikely to be explained by smoking differences.**

Keywords occupational lead, mortality, cancer incidence

Key Messages

- Here, we seek to determine whether cancer incidence increases with higher blood lead in an occupational cohort.
- We provide evidence, via exposure–response analyses, that lead is associated with lung cancer.
- This finding could affect the classification of lead, currently considered as a probable carcinogen.

Introduction

Environmental exposure to inorganic lead in the USA has decreased substantially since the 1970s with the elimination of lead from gasoline and paint [1–3]. However, there remain substantial numbers of US workers who have been exposed occupationally, now and in the past. An estimated 3 million US workers were exposed to lead in 1998 [4] and the National Institute for Occupational Safety and Health (NIOSH) estimated in 2018 that ∼800 000 workers were exposed in general industry and another 800 000 in construction [5].

Current US Occupational Safety and Health Administration standards require workers to be removed from lead exposure when their blood lead level reaches 50 μg/dL (construction workers) or 60 μg/dL (other workers) and to not return to work until their blood lead levels are <40 μg/dL. However, current standards may be outdated and not adequately protect workers' health [6–8]; some have suggested that workers should be removed from lead exposure when their blood levels reach 20 μg/dL [9].

The health effects of lead have been observed in all organ systems over a wide range of lead levels [4]. Most general-population studies have studied cardiovascular morbidity and

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have shown that increasing blood levels are related to higher blood pressure, higher heart disease incidence [10–12], and higher cardiovascular mortality [9–15].

Inorganic lead was classified as a 'probable human carcinogen' by the International Agency for Research on Cancer (IARC) in 2006 [16] based on sufficient evidence in animals and limited evidence in humans. The National Toxicology Program in 2016 found similar results [17]. The IARC has recommended lead as a priority for future research [18]. Studies examining the relationship between lead and cancer have largely been among occupational populations, who have much higher average lead levels than the general population. Most have been mortality studies; there are only a few occupational studies on cancer incidence [19] and none in the USA.

We previously followed a large cohort of lead-exposed workers ($n = 58\,368$) for mortality over 19 years [5]. We have now added 4 years of follow-up (extending from 2017 to 2021) for mortality analyses.

While we report our updated mortality results, our focus in this paper is on the cancer incidence in a subset of our cohort using the newly created Virtual Pooled Registry Linkage System (https://www.apps.naaccr.org/vpr-cls/), which facilitates cancer-incidence follow-up across numerous state registries. The subset ($n = 37\,547$) was chosen because they had complete social security numbers (SSNs) as well as current addresses obtained from Nexis-Lexis, a USA-based firm providing extensive databases on individuals (https://www.lexisnexis.com/en-us), enabling better matching to state cancer registry data.

Methods

Data sources/study cohort

The cohort is formed from workers who were enrolled in the Adult Blood Lead Surveillance (ABLES) program sponsored by the National Institute for Occupational Safety and Health [20]. ABLES has tracked laboratory-reported cases of elevated blood lead levels in US adults since 1987. Blood lead tests were generally conducted subsequent to occupational exposure; for example, during 2003–4, 94% of adults with blood lead levels reported to ABLES were exposed via occupational sources [20]. Non-occupational exposure, largely at background levels, was largely due to women being tested for possible exposure to lead paint and concern over the effects on their children; we restricted our cohort to men. The ABLES coverage increased from 4 US states in 1987 to 41 states in 2012.

The cohort consisted of male workers from 11 US states who had had at least one blood lead level reported to ABLES before 2005. The states included California, Connecticut, Iowa, Massachusetts, Michigan, Minnesota, New Jersey, New York, Ohio, Pennsylvania, and Wisconsin; they were chosen because they had the most subjects with blood lead data and data that went back the furthest in time. All men who had ever had a blood lead level of ≥ 25 μg/dL were included, while workers whose highest blood lead level was either <5 or 5 to <25 μg/dL were randomly selected proportionally across states within the blood lead category (50% selected in each state). The final study cohort consisted of 58 368 workers, who were analysed for mortality.

For cancer mortality, we used name, date of birth, sex, state of residence at the time of ABLES test(s), race (when available), and SSN (when available) for matching with the National Death Index (NDI) through to the end of 2021. We defined a match as any worker found in the NDI with an NDI status code of 1 (indicating a high probability of a true match). Among workers who had died, we used the ICD9/10 code indicated as the primary cause of death to determine cause-specific mortality (Supplementary Table 1). We present results for 16 specific causes of death [12 cancer causes, chronic obstructive pulmonary disease (COPD), ischemic heart disease, stroke, and chronic renal disease].

For our cancer-incidence analysis, we worked with the recently created Virtual Pooled Registry Cancer Linkage System (VPR), coordinated by the North American Association of Central Cancer Registries and funded by the National Cancer Institute (NCI). The VPR facilitates the linkage of cohorts with multiple US cancer registries, simplifying cancer-incidence follow-up studies.

For the cancer-incidence analysis, we first obtained further identifying information in 2023 from Lexis-Nexis, using all the identifying information we had, which consisted of name, date of birth, and state in which workers had been tested, as well as race for 31% and SSN for 34% of the cohort, and date of death for 6527 (11%), the last based on our prior mortality follow-up [5]. Lexis-Nexis provided us with most current address and SSN for 37 546 men. This further identifying information was needed in order to accurately use the VPR. From this sub-cohort, we then excluded workers whose first blood lead level measurement occurred after their first cancer diagnosis date ($n = 256$) and excluded workers currently living in one state from which we were ultimately unable to obtain cancer data (Alabama). In Washington state, we excluded any men living in counties not covered by the Seattle Cancer Registry (61% of the state's population is covered). However, men most recently residing in these excluded states who were found to have been diagnosed in a different state were retained in the analysis. This left a final cohort for analysis of 36 979 (98% of the original 37 546 men with incidence data and 63% of the mortality cohort). Multiple primary cancers for the same men occurred in 15% of the workers and were treated independently in the cancer-specific analyses. Cancer-incidence follow-up went through 2021 for most states, although for one (New York), it went only through 2020.

Variables

The name, date of birth, date of each blood lead test, and blood lead level (in μg/dL) for each blood lead test were collected from the selected male workers in each of the 11 US states. We categorized each person into one of four blood lead categories based on the highest blood lead level that they had recorded in the ABLES program: <5, 5 to <25, 25 to <40, or ≥ 40 μg/dL.

Missing race was imputed five times via simulations (using Proc MI in SAS), five separate regression models were run, and coefficients and standard errors were averaged (see the Supplementary Material from Chowdhury *et al.* [21]).

For cancer incidence, we used the same ICD9/10-based classification for the primary site, with the exception of hematopoietic cancer, for which we used the NCI Surveillance, Epidemiology, and End Results (SEER) recode system, based on histology, to classify cancers into four primary categories; leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and myeloma.

For those men with more than one blood lead test, we assigned to them the blood level of their highest test to use in analyses.

Statistical analysis of mortality and cancer-incidence data: exposure–response analyses

Cox proportional hazards regression (via SAS) was used to calculate hazard ratios (HRs) associated with each lead category within the cohort (i.e. internal analyses) after adjusting for birth year (5-year categories) and race, using age as the timescale. For the mortality analysis, the person-time at risk began at the time of the first blood lead ABLES test and continued either to the date of death or 31 December 2021. For the cancer-incidence analysis, the person-time began at the time of the first blood lead test and ended when an incident cancer occurred, death occurred, or at the end of follow-up on 31 December 2021 (31 December 2020 for New York). Multiple primary cancers were considered independently, following cancer registry guidelines; ∼15% of the subjects had multiple cancers. For example, if a person had colon cancer followed by a lung cancer that was a second primary, in the analysis for colon cancer, the person-time stopped at the date of the colon cancer diagnosis, while stopping at the time of the lung cancer diagnosis for the lung cancer diagnosis.

Categorical analyses compared the rate at each of the blood lead categories to the reference category, which was either <5 or 0 to <25 μg/dL (depending on whether there were <10 cases in the lowest <5 μg/dL category). *P* values to describe trends were generated for each cause of death with Cox proportional hazards regression models that used either logged or unlogged continuous blood lead as the exposure. Linear and log-linear variables are among the most common parameterizations of continuous exposure variables in environmental/occupational epidemiology. Log-linear transformations tend to capture trends that tail off at higher exposures, which is common in environmental/occupational epidemiology. Akaike's Information Criterion (AICs) were used to assess fit.

The study was approved by the Emory University Institutional Review Board.

Results

Cohort

The characteristics of the entire cohort are described in Table 1. Among the 58 368 male workers in the cohort, only 31% had race information, among whom 80% were White. After imputation [5], 83% were White. The median year of birth was 1959 (range, 1914–93). Workers were 39 years old, on average, at the time of their first blood lead test in 1998. The median follow-up for the cohort was 23 years and there were a total of 8832 deaths (15%) during the follow-up time period. Nearly half of the cohort (47%) were from either New York or California, based on their current address, with the rest from the other nine states.

Half of the cohort (49%) had had only one blood lead test. Among workers with more than one blood lead test, the median number of blood lead tests per person was four.

Table 1 Description of cohort for mortality analysis (*N* = 58 368).

	Highest lead category achieved				
Characteristics	**0 to <5 μg/dl]**	**[5 to < 25 μg/dl]**	**[25 to < 40 μg/dl]**	**[40+ μg/dl]**	**Total**
Number in cohort	6848 (12%)	18 650 (32%)	21 448 (37%)	11 422 (20%)	58 368
Median years of follow-up	17.39	20.76	24.55	27.07	22.50
Mean age at first test in years	40.72	39.99	37.90	38.31	38.98
Race					
White	1448 (21%)	2356 (13%)	6246 (29%)	4339 (38%)	14 389 (25%)
Non-white	252 (4%)	558 (3%)	1673 (8%)	1200 (10%)	3683 (6%)
Missing/Unknown	5148 (75%)	15 736 (84%)	13 529 (63%)	5883 (52%)	40 296 (69%)
Race imputed					
White	6026 (88%)	15 014 (81%)	17 898 (83%)	9478 (83%)	48 357 (83%)
Non-white	806 (12%)	3604 (19%)	3542 (17%)	1940 (17%)	9891 (17%)
Median number blood tests in those with >1 test	2	3	4	6	4
Number with single tests only	6124 (89%)	12 739 (68%)	7786 (36%)	1940 (17%)	28 589 (49%)
Mean highest blood lead level	2.46	12.97	30.79	52.01	25.93
Median year of first lead test	2004	2000	1996	1992	1998
Median year of birth	1962	1961	1959	1955	1959
Median year of death	2014	2014	2013	2011	2013
Number of deaths	651 (10%)	2121 (11%)	3339 (16%)	2721 (24%)	8832 (15%)

Table 2 Cohort demographics for cancer-incidence analysis (N = 36 077).

Characteristics	Highest lead category achieved				
	1 (0 to <5 μg/dL)	2 (5 to <25 μg/dL)	3 (25 to <40 μg/dL)	4 (≥40 μg/dL)	Total
Number in cohort[a] [*n* (%)]	4156 (11)	10 877 (29)	13 990 (38)	7956 (22)	36 979
Median years of follow-up	17.17	20.36	24.28	26.69	22.22
Mean age at first test in years	40.53	39.46	36.64	37.21	38.05
Race [*n* (%)]					
White	902 (22)	1590 (15)	4898 (35)	3568 (45)	10 958 (30)
Non-White	172 (4%)	387 (3)	1396 (10)	1033 (14)	2988 (8)
Missing/unknown	3082 (74%)	8900 (82)	7696 (55)	3355 (41)	23 033 (62)
Race imputed [*n* (%)]					
White	3984 (96)	10 490 (96)	12 594 (90)	6923 (87)	33 991 (92)
Non-white	172 (4)	387 (4)	1396 (10)	1033 (13)	2988 (8)
Median number of blood tests in those with >1 test	2	3	4	6	4
Number with single tests only [*n* (%)]	3667 (88)	7093 (65)	4779 (34)	1248 (16)	16 787 (45)
Mean highest blood lead level	2.42	12.46	30.78	51.93	26.75
Median year of first lead test	2004	2000	1995	1991	1997
Median year of birth	1962	1960	1958	1955	1958
Median year of cancer diagnosis[b]	2014	2012	2011	2008	2011
Number of cancers[c] [*n* (%)]	436 (11)	1593 (15)	2266 (16)	1830 (23)	6125 (16)

[a] Subjects without SSN, cancer diagnosis date before exposure date.
[b] For subjects diagnosed with multiple cancers, the year of diagnosis was for their first cancer case.
[c] This includes multiple cancer cases.

The cohort characteristics for the incidence analysis are shown in Table 2. Generally, this subset followed for incidence (61% of the mortality cohort) shared the characteristics of the full cohort.

Mortality analyses

In internal analyses, there were significant trends ($P \leq .05$) of increased risk at higher exposure for all-cause, lung cancer, pancreatic cancer, ischemic heart disease, chronic renal disease, and COPD mortality, with the lung cancer trend being the most marked (Tables 3 and 4 using a collapsed referent group when events were fewer). Borderline positive trends ($.05 < P \leq .10$) were found for larynx, liver, bladder, and rectal cancer. Tables 3 and 4 include analyses using multiple causes (any cause on the death certificate) for some causes. Multiple-cause analyses of kidney disease, COPD, and ischemic heart disease also showed significant positive trends.

Cancer analyses

A strong positive trend was seen was seen for lung cancer ($P < .01$), with a high HR (2.43) in the highest category (Tables 5 and 6). Liver cancer showed significant positive trends (P value of .05 to .10). In contrast, negative trends were seen for prostate and thyroid cancer (both $P \leq .01$).

Discussion

Mortality

The mortality results showed positive significant trends for lung cancer, pancreatic cancer, heart disease, COPD, and chronic renal disease. There were borderline trends with bladder, brain, liver, larynx, and rectal cancer. Prior mortality follow-up [5], with 4 fewer years of follow-up, showed similar results. The prior follow-up also found significant positive mortality trends with lung cancer, heart disease, and COPD, with borderline positive trends for larynx and brain cancer, a positive trend for pancreatic cancer ($P = .15$), as well as excesses of liver cancer, rectal, and bladder cancer in the highest-exposure category. Non-Hodgkin's lymphoma showed positive trends in both follow-ups ($P = .06$ for the prior follow-up, $P = .13$ in the current one). Of note from the new mortality update is the significant positive trend for chronic renal disease mortality, which has been associated with lead in other studies, including those of lead and end-stage renal disease risk or reduced kidney function [21–24]. The current follow-up had twice the number of chronic renal disease deaths as the prior one. The renal disease trend was also seen when using multiple-cause data.

Cancer incidence

Our cancer-incidence results supported a strong positive trend for lung cancer and a significant positive trend for liver cancer. On the other hand, incidence analyses showed negative trends

Table 3 Mortality HRs and 95% confidence intervals (CIs) by lead category with 0 to <5 μg/dL as the referent group and mortality analysis using underlying cause and multiple causes of death (for causes with ≥10 deaths in the referent group of <5 μg/dL).

	Highest lead category achieved (μg/dL)								*P* value for test for trend[a,c]	*P* value for test for trend[b,c]
	0 to <5		5 to <25		25 to <40		≥40			
Cause of death	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)		
All causes	594	Reference	2121	1.00 (0.92, 1.10)	3339	**1.11 (1.02, 1.20)**	2721	**1.38 (1.26, 1.50)**	**<.01**	**<.01**
Cancer										
Esophagus	10	Reference	25	0.78 (0.37, 1.62)	35	0.85 (0.42, 1.72)	30	1.17 (0.57, 2.43)	.48	.39
Kidney	11	Reference	18	0.51 (0.24, 1.08)	18	0.40 (0.19, 0.85)	17	0.61 (0.28, 1.31)	**.10**	.66
Liver	12	Reference	41	1.09 (0.57, 2.08)	47	0.94 (0.50, 1.79)	55	1.79 (0.95, 3.37)	**.10**	**.08**
Lung	30	Reference	167	**1.64 (1.11, 2.41)**	324	**2.16 (1.48, 3.14)**	312	**3.00 (2.05, 4.37)**	**<.01**	**<.01**
Stroke	21	Reference	58	0.81 (0.49, 1.34)	119	1.07 (0.67, 1.71)	96	1.22 (0.75, 1.98)	.50	.16
COPD	28	Reference	81	0.86 (0.56, 1.33)	175	1.32 (0.88, 1.96)	161	**1.78 (1.19, 2.68)**	**<.01**	**<.01**
Ischemic heart disease	94	Reference	313	0.99 (0.79, 1.25)	570	1.22 (0.98, 1.52)	451	**1.40 (1.12, 1.76)**	.14	**<.01**
Stroke (multiple causes)	28	Reference	81	0.89 (0.58, 1.36)	151	1.09 (0.72, 1.63)	116	1.23 (0.93, 1.09)	.82	.24
COPD (multiple causes)	36	Reference	132	1.12 (0.78, 1.62)	249	**1.54 (1.09, 2.19)**	216	**2.03 (1.43, 2.91)**	**<.01**	**<.01**
Ischemic heart disease (multiple causes)	112	Reference	361	0.98 (0.79, 1.21)	640	1.19 (0.97, 1.46)	500	**1.38 (1.12, 1.70)**	.11	**<.01**

[a] From proportional hazards regression model with log continuous blood lead as the exposure (adjusted for calendar time period and race with age as the timescale).
[b] From proportional hazards regression model with linear continuous blood lead as the exposure (adjusted for calendar time period and race with age as the timescale).
[c] Trend test with lower *P* value had lower AIC, i.e. had better fit. Trend *P* values in bold if *P*≤.10. HRs in bold if CI excludes 1.00.

Table 4 Mortality HRs and 95% confidence intervals (CIs) by lead category with 0 to <25 μg/dL as the referent group, using underlying cause and multiple causes of death (for causes with <10 deaths in the <5 μg/dL category).

	Highest lead category achieved (μg/dL)						*P* value for test for trend[a,c]	*P* value for test for trend[b,c]
	0 to <25		25 to <40		≥40			
Cause of death	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)		
Cancer								
Colon	40	Reference	57	1.24 (0.82, 1.87)	46	1.47 (0.94, 2.28)	.53	.19
Stomach	16	Reference	15	0.70 (0.34, 1.45)	18	1.15 (0.56, 2.35)	.91	.67
Brain	21	Reference	30	1.40 (0.80, 2.47)	16	1.17 (0.60, 2.29)	.31	.67
Bladder	18	Reference	28	1.35 (0.74, 2.45)	29	**2.01 (1.10, 3.69)**	.98	**.06**
Larynx	7	Reference	8	0.99 (0.35, 2.75)	15	**2.78 (1.09, 7.05)**	.27	**.07**
Non-Hodgkin's lymphoma	27	Reference	27	0.85 (0.49, 1.47)	32	1.47 (0.85, 2.52)	.15	.13
Pancreatic	52	Reference	58	1.06 (0.72, 1.54)	47	1.30 (0.87, 1.96)	**.04**	**.02**
Rectal	14	Reference	19	1.26 (0.63, 2.54)	19	1.92 (0.94, 3.91)	.75	**.07**
Chronic renal disease	23	Reference	38	1.38 (0.82, 2.34)	36	**1.92 (1.12, 3.29)**	.13	**.02**
Chronic renal disease (multiple causes)	56	Reference	70	1.12 (0.78, 1.60)	67	**1.63 (1.13, 2.34)**	.21	**.05**

[a] From proportional hazards regression model with log continuous blood lead as the exposure (adjusted for calendar time period and race with age as the timescale).
[b] From proportional hazards regression model with linear continuous blood lead as the exposure (adjusted for calendar time period and race with age as the timescale).
[c] Trend test with lower *P* value had lower AIC, i.e. had better fit. Trend *P* values in bold if *P*≤.10. HRs in bold if CI excludes 1.00.

Table 5 HRs and 95% confidence intervals (CIs) for incident cancer by lead category with 0 to <5 μg/dL as the referent group.

	Highest lead category achieved (μg/dL)								*P* value for test for trend[a,c]	*P* value for test for trend[b,c]
	0 to <5		5 to <25		25 to <40		≥40			
Cancer	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)		
Bladder	25	Reference	99	1.27 (0.81, 1.98)	153	1.27 (0.82, 1.96)	115	1.39 (0.89, 2.17)	.93	.47
Brain	11	Reference	45	1.96 (0.88, 4.36)	54	1.53 (0.69, 3.38)	30	1.32 (0.57, 3.04)	.76	.18
Colon	27	Reference	84	0.95 (0.61, 1.46)	122	0.84 (0.55, 1.28)	122	1.21 (0.79, 1.86)	.75	.21
Kidney	23	Reference	67	0.92 (0.57, 1.48)	91	0.81 (0.51, 1.29)	83	1.11 (0.69, 1.78)	.44	.75
Leukemia	25	Reference	91	1.22 (0.77, 1.94)	113	0.93 (0.59, 1.47)	86	1.03 (0.64, 1.65)	.89	.18
Liver	11	Reference	41	1.32 (0.66, 2.65)	57	1.28 (0.65, 2.52)	61	**2.11 (1.08, 4.15)**	**.03**	**.02**
Lung	33	Reference	224	**2.04 (1.40, 2.98)**	363	**2.07 (1.43, 2.99)**	341	**2.66 (1.83, 3.85)**	**<.01**	**<.01**
Non-Hodgkin's lymphoma	21	Reference	63	0.88 (0.53, 1.44)	76	0.68 (0.42, 1.11)	62	0.84 (0.50, 1.40)	.72	.95
Prostate	137	Reference	414	0.97 (0.79, 1.18)	562	**0.82 (0.68, 1.00)**	392	**0.79 (0.65, 0.97)**	**.04**	**<.01**
Rectal	11	Reference	48	1.33 (0.69, 2.57)	85	1.50 (0.79, 2.83)	70	1.79 (0.93, 3.42)	.39	.13
Thyroid	19	Reference	39	0.76 (0.43, 1.34)	43	0.59 (0.33, 1.04)	24	0.56 (0.30, 1.06)	**.01**	**.02**

[a] From proportional hazards regression model with log continuous blood lead as the exposure (adjusted for calendar time period and race with age as the timescale).
[b] From proportional hazards regression model with linear continuous blood lead as the exposure (adjusted for calendar time period and race with age as the timescale).
[c] Trend test with lower *P* value represents the model with better fit. Trend *P* values in bold if $P \leq 10$. HRs in bold if CI excludes 1.00.

Table 6 HRs and 95% confidence intervals (CIs) by lead category for incident cancer with 0 to <25 μg/dL as the referent group, for cancers with sparse data (<10) in the <5 μg/dL category.

	Highest lead category achieved (μg/dL)						*P* value for test for trend[a,c]	*P* value for test for trend[b,c]
	0 to <25		25 to <40		≥40			
Cancer	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)		
Esophagus	37	Reference	44	1.09 (0.70, 1.70)	33	1.23 (0.75, 1.99)	.78	.66
Larynx	35	Reference	44	1.08 (0.69, 1.70)	32	1.15 (0.70, 1.90)	.89	.80
Myeloma	19	Reference	16	0.71 (0.35, 1.40)	15	0.95 (0.46, 1.94)	.78	.99
Pancreatic	56	Reference	53	0.78 (0.53, 1.15)	43	0.94 (0.62, 1.43)	.36	.42
Stomach	35	Reference	37	0.85 (0.52, 1.36)	27	0.90 (0.53, 1.53)	.57	.71
Testicular	17	Reference	17	0.68 (0.32, 1.46)	11	0.90 (0.39, 2.11)	.09	.68

[a] From proportional hazards regression model with log continuous blood lead as the exposure (adjusted for calendar time period and race with age as the timescale).
[b] From proportional hazards regression model with linear continuous blood lead as the exposure (adjusted for calendar time period and race with age as the timescale).
[c] Trend test with lower *P* value represents the model with better fit.

for two cancers (thyroid and prostate). These cancers rarely cause deaths and were too few to be analysed in the mortality analyses.

Our lung cancer findings are consistent with previously reported positive associations between lead and lung cancer incidence in occupational studies [20, 25–27], as well as some positive evidence in a population-based study [28]. Like other studies, we cannot exclude the possibility of interaction or confounding by occupation-related carcinogenic co-exposures (such as arsenic or engine exhaust) [27]. However, the workers in our cohort worked in various industries/jobs (see below) with different co-exposures, making it less likely that one specific co-exposure would fully explain our results.

Smoking may also confound the associations found between lead and lung cancer mortality or interact with lead to increase lung cancer risk. However, if the lung incidence findings were due to smoking, then we would have expected similar associations with larynx cancer incidence (typically associated with smoking), which we do not see. While we do see an association between blood lead and COPD mortality, another strongly

smoking-related disease, there is some evidence showing that lead exposure may be directly associated with COPD [29, 30].

Additionally, internal analyses comparing workers to workers are generally less susceptible to confounding by smoking [31, 32, 33] and our internal analyses for lung cancer incidence (and mortality) showed strong effects with the blood lead level category (i.e. HRs of 2–3 when comparing highest- to lowest-exposure categories), which are very high to be potentially explained by confounding by smoking [31]. For example, if the RR (rate ratio) for ever-smoking and lung cancer were 15, and if 40% of the highest exposed workers smoked vs 20% of the lowest exposed, smoking differences would only explain an elevated RR of 1.43 between high vs low exposed. In occupational studies comparing workers to workers, such extreme smoking differences are very unlikely [34].

Furthermore, our workers came from many different industries, making it less likely that smoking patterns linked to the exposure level in one industry would also be so across other industries. Very limited data were available on industries. NIOSH collected data on the industries of employment for a limited number of ABLES subjects ($n = 6999$) with blood lead levels of $\geq$25 mg/dl in 2009 [34]. Of these, 62% were in manufacturing [primarily storage batteries (36%), secondary smelting (13%), primary battery (5%)], 10% were in construction [primarily painting (6%)], 7% were in metal mining (primarily lead/zinc ores), 1% were in trade (scrap and waste materials), and 20% were in other industries or data were unavailable [34].

Finally, when a sample of this cohort ($n = 211$ workers) were interviewed about smoking, there was no correlation between the maximum past blood lead level and the pack-years of smoking, with a correlation of 0.0 ($P = .98$) (unpublished data, see [35] for background on this study).

Our results show some evidence of an association between lead and an increased incidence of brain cancer, although the incidence trend ($P = .18$) was not significant. The IARC determined in 2006 that brain cancer was one of the more strongly associated outcomes related to inorganic lead (IARC 2006) and other studies since then have also shown associations between lead and brain cancer [18, 19, 36–38].

We found a significant positive trend between lead levels and liver cancer incidence, and a borderline trend for liver cancer mortality. There is scant evidence of an association between lead and liver cancer in the literature. However, in recent years, there have been a number of reports of lead exposure, both in the general population and in occupational settings, associated with alternations of liver enzymes or with increases in non-alcoholic liver disease, the latter being associated with liver cancer [39–42]. There is also one report, based on small numbers, of a significant positive association between occupational lead levels and liver cancer mortality [43].

Our study has several strengths. First, it is a large cohort of lead-exposed workers with documented blood lead levels. Having a cohort with internal doses at an individual level can be an advantage, as most studies do not have individually measured internal exposure. Second, we have studied cancer incidence, which is preferable to regarding etiologic inference, as it is not as dependent on the quality of and access to treatment.

This study also has several limitations. First, the exposure is the blood lead level, which reflects only recent exposure (i.e. in the previous few months) to lead and does not allow characterization or cumulative exposure. However, in a study using a subset of this cohort, past maximum blood lead was correlated with current (i.e. 2017–18) bone lead (R^2=0.27, $P < .01$); the latter is a measure of cumulative exposure and we believe that our broad exposure categories are likely to be accurate [35]. Our lack of complete work history precludes us from knowing when the person-time at risk due to lead exposure actually began, making it impossible to accurately analyse by lags, which are important, as most cancers will take many years to develop. Across our cohort for cancer incidence, we had an average of 14 years between the date of the first blood lead test and the date of the cancer diagnosis, suggesting that, in many cases, a reasonable lag was operating. Our lack of coverage across all states (partly due to some not being part of the VPR) make our conclusion slightly less generalizable. Finally, our study is restricted to men by the nature of our surveillance data and it is not known whether our findings would be similar in women.

Conclusion

Our cancer-incidence findings support an association with lung cancer and also a significant association with liver cancer. There is some modest support for an association with brain cancer.

Ethics approval

This study was approved by the Emory University Institutional Review Board.

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Author contributions

All authors contributed to the writing and editing of the manuscript. Y.T. conducted the analysis.

Supplementary material

Supplementary material is available at *IJE* online.

Conflicts of interest

None declared.

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Data availability

These data are from the NIOSH ABLES program. De-identified data from our analysis can be obtained from the authors only with permission from the NIOSH ABLES program. 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.

Use of artificial intelligence (AI) tools

No AI has been used in the preparation or writing of this paper.

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