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Elevated Blood Lead Levels, Cancer Incidence, and All-Cause Mortality in Adults

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EPIDEMIOLOGY

ABSTRACT

Epidemiologic studies have indicated an association between lead exposure and cancer. Although lead exposure has declined in recent decades, from removal of lead in gasoline and paint, lead exposure remains a health concern from environmental and occupational sources including aging water systems.

In a retrospective cohort study, Adult Blood Lead Epidemiology and Surveillance (ABLES) records in Alabama were linked to cancer incidence data in the Alabama Statewide Cancer Registry and mortality data from the Alabama Center for Health Statistics, using a probabilistic linkage program. Blood lead level (BLL) measurements were used to categorize exposure levels. Odds ratios approximated relative risks. Logistic regression assessed dose-response across five exposure levels (highest ≥40 µg/dL) compared to baseline exposure (<5 µg/dL). Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) were calculated using the Alabama population to estimate expected cases of "any cancer"; cancers of the bladder, brain, kidney, lung, and stomach; and expected deaths. SIRs for males in the highest exposure groups were compared with SIRs from a published study of cancer incidence in New Jersey's ABLES cohort.

Of 14,274 individuals in the Alabama ABLES cohort, those highly exposed to lead had significantly increased odds of developing cancer (OR = 2.2), kidney cancer

(OR = 3.5), and lung cancer (OR= 3.2), comparing high (≥10 µg/dL) to baseline exposure. Significant trends across five exposure levels indicated dose-response. The odds of kidney cancer increased with dose but did not reach statistical significance. The ABLES cohort exhibited fewer cancer cases and fewer deaths than expected based on Alabama's cancer incidence and overall mortality rates, suggesting a healthy worker effect. The cancer SIRs for Alabama ABLES males and New Jersey ABLES males were strikingly similar, with ~50% fewer cancer cases observed in the respective ABLES cohorts than were expected.

Individuals in the Alabama ABLES cohort with elevated BLL have a statistically significant increased odds of cancer, lung cancer, and kidney cancer, compared to those minimally exposed, exhibiting dose-response across five levels of lead exposure. Similarities to the New Jersey ABLES analysis suggest that our results are reliable, and that lead is a risk factor for cancer.

Keywords: lead exposure, BLL, cancer, occupational, data linkage, surveillance

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INTRODUCTION

Background and Significance

The consequences for children with elevated blood lead levels are well established and include impaired cognitive development and ability, and damage to the nervous system even at levels below 5 µg/dL.[1,2] In adults, the effects are not as certain, but lead exposure is known to damage nerves, impair cognitive function and coordination, and increase blood pressure.[1] Despite lead being recognized as a harmful substance if ingested or inhaled, it is still unclear whether lead exposure contributes significantly to the burden of cancer. With the recent crisis in Flint, MI, it is now, more than ever, critical to understand the consequences of lead exposure.[3]

In the 21st century, exposure to lead remains a threat to health in the United States. Although lead-based paints were banned in 1976 by the Consumer Product Safety Commission, and the Clean Air Act removed lead from gasoline by 1995, lead exposure still occurs. Banning lead from paint manufacturing did not remove it from the dwellings already painted with lead-based paint. Non-residential lead paint exposures may arise from imported toys, cookware, aged water system piping, some traditional cultural medicines (e.g., used as an eye cosmetic that is believed to improve vision and strengthen eyes), and imported candies. Occupations at highest risk include battery recycling and smelting, construction work, and even firing range employees where dust from lead ammunition becomes airborne. Despite an overall decline in lead exposure, a health

concern remains because of exposure from occupational sources, the environment, and aging water systems.

Lead as a Carcinogen

The National Toxicology Program (NTP) Report on Carcinogens (14th Edition) classifies lead as "reasonably anticipated to be [a] human carcinogen."[4] As of 2006, the International Agency for Research on Cancer (IARC) classified inorganic lead compounds as "probably carcinogenic to humans" and organic lead compounds as "not classifiable as to their carcinogenicity to humans."[2] However, IARC also acknowledged that organic lead compounds such as tetraethyl lead and tetramethyl lead, are metabolized to ionic lead and can thus become as toxic as inorganic compounds.[2] In 2014, IARC listed lead as a "medium priority" regarding its carcinogenic risk to humans to be reexamined before 2019.[5] Epidemiologic studies reviewed by IARC have shown inconsistent results, ranging from weak associations with various cancers (especially lung, digestive, kidney, and brain cancers), to no associations or protective associations; animal models demonstrated inconsistent positive associations.[2]

It is logical to consider the bladder, brain, kidneys, and stomach as potential sites for lead carcinogenesis. The health effects related to elevated lead levels in these organs have been documented by the Agency for Toxic Substances and Disease Registry (ATSDR), NTP and IARC.[1,2,4] Several studies have found associations between lead exposure and kidney damage, kidney disease, and kidney cancer.[6-12] The kidneys and brain are considered to be target organs for lead in the blood.[2]

Lead can Cause DNA Damage and Disrupt DNA Repair Mechanisms

Lead exposure is associated with DNA damage and prevention of DNA repair in rats and humans.[2] DNA alterations may allow for the development of cancers, depending on the genes affected. One recent case-control study using the National Cancer Institute Brain Tumor Study data approximated lead exposure based on job history and found that individuals with lead exposure and meningiomas, or glioblastoma multiforme had increased odds of polymorphisms of two glutathione peroxidase-1 (GPx1) genes.[13] GPx1 is known to protect tissues from oxidative damage and decrease DNA mutagenesis.[14] In a cohort study, Wu et al. compared 57 lead workers in Taiwan with controls having no lead exposure, matched by age and smoking status, to assess cytogenic damage. Biomarkers assessed the damage. The mean DNA-protein cross-links (DPCs) and sister chromatid exchanges (SCEs) for workers with lead exposure were significantly higher than for the controls ($p < 0.01$). DPC and SCE significantly increased with BLL levels. Disruption in DNA repair mechanism leads to malignant transformations and cancer development.[15,16]

Lead Exposure, Cancer Morbidity and Mortality

Occupational lead exposure and cancer morbidity. Most cohort and case-control studies assessing lead exposure and health outcomes rely on assumptions about lead burden or calculate lead exposure based on employment or occupational history.

Four such case-control studies of Canadian populations examined occupational history or job descriptions; stomach (gastric) cancer associations are identified in three of the four studies. In 1988, Risch et al. indicated a significant increased odds of developing

bladder cancer for individuals whose occupational history indicated they had ever been exposed to lead compounds. A positive trend with duration of exposure was also observed.[17] Analysis of the Montreal Occupational Cancer Study noted incidence of gastric cancer and lung cancer were statistically significantly elevated in individuals having substantial lead exposure. This nested case control study found that men with gastric cancer were more likely to have been exposed to crystalline silica, leaded gasoline, grain dust, lead dust, zinc dust, hydraulic fluids, and glycol ethers at their jobs as compared to men without gastric cancer.[18] Rousseau et al. reviewed population-based data to assess the lead exposure of cases with 11 kinds of cancer compared to population controls and case controls; the case controls were individuals diagnosed with other cancers. Exposure to lead was assigned algorithmically based on occupation. Brain cancer was not one of the 11 cancers examined; however, bladder, kidney, lung, and stomach cancer were assessed. Stomach cancer was found to be associated with organic lead exposure: OR 3.0 (1.2, 7.3) compared with population controls and OR 2.0 (1.1, 3.8) compared with controls diagnosed with other cancers (i.e., cancer controls). Stomach cancer was also associated with substantial lead exposure from gasoline emissions when compared with cancer controls: OR 2.9 (1.4, 5.9). So, there is evidence of a 2-3-fold increased risk of stomach cancer which has an overall case fatality rate of 71% according to the American Cancer Society.[19]

A population-based case-control study in Germany looking at renal cell carcinoma and occupation found significantly elevated odds for men and women with substantial exposure to lead (ORs 1.5 and 2.6, respectively).[10] A case-control study in China by Hu et al. considering occupational exposures and meningiomas found a positive

association with reported occupational exposures to lead in men and women (ORs 7.2 and 5.7, respectively).[20]

Occupational lead exposure and cancer mortality. Six recent studies of cohorts in the U.S. assessed mortality data as it relates to occupational lead exposure recorded in employment records. The study findings included significant associations between occupational lead exposure and cancer, specifically kidney, digestive, lung, and brain cancers. In a longitudinal cohort study by van Wijingaarden and Dosemeci assessing brain cancer mortality in the non-institutionalized U.S. population in 1979-1989 according to occupation and industry, individuals more likely to be exposed to lead had a higher hazard ratio for brain cancer than those not exposed.[21] In 2000, Wong and Harris updated a previous cohort study that evaluated cancer mortality of employees at lead battery plants and lead smelters, extending the follow-up time for mortality from 1980 to 1995. Overall, the standardized mortality ratio was significantly higher in the employees of the lead battery plants for cancer of the stomach.[22] Yet, a nested case control study of the stomach cancer cases and selected controls did not find an association with lead exposure.[18] Steenland et al. revisited a retrospective cohort of male smelter workers including 11 additional years of follow-up data on deaths. In that study, kidney cancer deaths remained excessive in individuals with a longer exposure to lead.[12]

Using a case-control design, Cocco et al. assessed death certificate records from 24 U.S. states for cause of death due to gastric cardia cancer as may be related to exposures from occupation and industry. Probabilistic logic was applied to occupation to determine odds of developing gastric cardia cancer based on likely exposure to selected

chemicals. White men in occupations with a high probability of lead exposure had a 30% increased odds of developing cancer of the gastric cardia (OR 1.3, CI 1.0, 1.7). When assessing likelihood of a high intensity level of exposure to lead based on occupation, odds of developing cancer of the gastric cardia was significantly higher (OR 1.6, CI 1.0, 2.8), compared with those without likely exposure to lead.[23]

A retrospective cohort in Great Britain by Malcolm and Barnett using the primary occupation at lead acid battery plants between 1925 and 1976 as the exposure of interest and mortality as the outcome did not find any significant excess deaths, overall or by any one category, when comparing the observed to the expected in the population.[24]

All in all, the data on lead exposure and cancer incidence drawn from several studies with varying study designs, and by independent investigators, suggests a causal association of mild to moderate strength. When some epidemiologic studies show positive associations, others show no associations, and a few others show protective effects, a common interpretation is that there is a positive association (probably, a causal one) that is difficult to establish statistically because the relative risk or odds ratio is typically something less than 1.5 (which would indicate a 50% elevation in risk). More subtle, but real, elevations in risk cannot be established unless the sample size is extraordinarily high. However, looking at all lead – cancer data across all studies, a tentative conclusion of causation with an elevated risk of cancer seems appropriate. For the cancers most affected by lead, only lung is common, with even a mild increased risk of great concern because the incidence and mortality rates for lung cancer are so high, as is the case fatality. For the other cancers that the evidence suggests are caused by lead, the public health importance is not their large numbers but their high case fatality (as for

bladder, brain, and stomach), making prevention through protection from lead, a public health goal. A second reason for differences in results from study to study may be difficulties in measuring lead exposure and lack of consistency across studies in how this is done.

Blood lead levels and cancer incidence. Of the recent studies using BLLs as the measure of exposure, increased risk of lung cancer was identified in a variety of populations with elevated BLLs in Sweden, Finland, and the U.S.[25-29] In a Finnish cohort study, the highest level of blood lead (collected 1973-1983) was linked to cancer incidence and mortality among 20,741 workers biologically monitored because of occupational exposure risks.[28] Individuals with elevated BLLs were 1.8 times more likely to develop lung cancer. Although several studies have mentioned a potential association between lead exposure and lung cancer, smoking data was not available, and a dose-response correlation was not apparent. Although information about smoking status, past or present is not available in the Adult Blood Lead Epidemiology and Surveillance (ABLES) data, lung cancer is included in the analysis since smokers have been shown to have higher lead levels attributable to the smoking.[30]

In a 2014 retrospective cohort study, Chowdhury et al. assessed all-cause mortality for men having elevated BLLs in 11 ABLES states: California, Connecticut, Iowa, Massachusetts, Michigan, Minnesota, New Jersey, New York, Ohio, Pennsylvania, and Wisconsin. Men with BLL greater than 40 μg/dL had an increased standardized mortality ratio (SMR) for lung (1.20) and laryngeal (2.11) cancers. Risk of lung cancer

mortality increased significantly as BLL increased. To date, this is the only study to identify an association of BLL with deaths from laryngeal cancer.[27]

In a Swedish retrospective cohort analysis conducted by Gerhardsson et al. of cancer incidence and mortality of lead smelter workers in 1942-1987, the group with the highest BLLs had a significant SIR of 2.34 for gastrointestinal cancers.[31]

Blood lead levels and cancer mortality. Several epidemiologic studies have investigated the general health effects of lead exposure that could lead to premature mortality. Health effects of concern include declining cognitive abilities, reproductive defects, cardiovascular illness, high blood pressure, stroke, cancer, and premature mortality, described in detail below. The National Health and Nutrition Examination Surveys (NHANES) data have been analyzed to assess health effects from lead exposure. Jemal et al. reported from the NHANES II dataset that when looking at whites only, no association between BLL and cancer mortality was observed; however, for women, a dose-response relationship was observed for cancer mortality with increasing BLL when using a spline dose-response analysis ($p = 0.001$).[32] To be noted, only cancer mortality, not cancer incidence, was studied. No cancer site-specific associations were identified. When the NHANES III data were assessed by Menke et al. for individuals over 20 years of age, no association between blood lead and cancer mortality was noted, though higher blood lead levels were significantly associated with overall deaths, cardiovascular diseases, myocardial infarctions, and stroke (HRs 1.25, 1.53, 1.78, and 1.59, respectively).[33] Yet, when Schober et al. reviewed the same dataset and limited it to individuals over 40 years of age, there was a significant association between elevated

BLLs and deaths from all-causes, cardiovascular disease, and cancer, so perhaps the younger cohort (20-40 yrs. old) included in the other study diluted its results.[34]

The Centers for Disease Control and Prevention (CDC) definition of elevated BLLs decreased from 25 µg/dL to 10 µg/dL in 2009, and further decreased to 5 µg/dL in 2016, in response to recommendations by the Council of State and Territorial Epidemiologist's Position Statement 15-EH-01: Public Health Reporting and National Notification for Elevated Blood Lead Levels, issued in 2015.[35] The National Institute for Occupational Safety and Health (NIOSH) also defines elevated blood levels as ≥5 µg/dL. Despite the threshold for excess lead in the blood being set at 5 µg/dL, it is generally accepted that there is no safe level of lead exposure.

However, the Occupational Safety and Health Administration's (OSHA) Regulations remain unchanged for the last 40 years, with action not required until the employees with known lead exposure have evidence of BLLs of ≥40 µg/dL. In recognition of documented adverse health effects in adults at levels <40 µg/dL, OSHA is "exploring regulatory options to lower blood leads in affected workers" while recommending actions at lower levels.[36-38] Lead industries, internationally, have set a year 2025 goal for employee BLLs to remain <20 µg/dL.[39]

Blood Lead Levels as Measure of Exposure

Lead has a half-life of approximately 25 days (up to 130 days for cumulative occupational exposure) in the blood; therefore, blood lead levels are a more accurate representation of lead exposure than assessing lead exposure based on occupational algorithms based on employment records and exposure probabilities. The benefit of

using the actual lead level is that we are not assuming or applying an algorithm to classify lead exposure, we are using the actual biologic measurement for that individual. With OSHA regulations in place in the U.S. that require personal protective equipment and limiting lead exposures (29 CFR 1910), it is difficult to apply the assumptions of exposure based on employment in today's work environment.

For adults, BLLs are measured testing venous whole blood. According to the Clinical Laboratory Improvement Amendments (CLIA) of 1988, the acceptable range for quality controls of BLL testing devices is ±4 μg/dL.[40] However, CDC's Advisory Committee on Childhood Lead Poisoning Prevention recommends that laboratories aim for greater precision, at ±2 μg/dL.

Strengths of our Study of Lead Exposure, Cancer, and Death from Any Cause

One benefit of our study is that we linked age of first elevated BLL report as an adult to the age at cancer diagnosis or death from any cause. With leaded gasoline elimination in the U.S., adults tested for suspected lead exposure, from occupational or non-occupational sources, are more likely to have lead levels distinctly different than the overall population not tested for lead exposure, making it easier to detect a significant difference.

A study in New Jersey similar to our study compared 3,200 individuals in their ABLES database to cancer cases recorded by their cancer registry and did not identify any significant positive associations.[29] Because Alabama's ABLES data 1990-2009 has five times the number of adults than NJ's ABLES database did at the time, there is greater power to detect a small effect size from our analyses.

The data linkage aspect of our study is invaluable and is an improvement over previous studies of chronic health outcomes of lead exposure. Many programs within public health, at the state and national level, store their data in siloed systems that do not communicate with each other. Each of the analyses within this study emphasize the value of system linkage to further public health knowledge and practice.

The objective of our study was to identify whether cancer incidence is an adverse outcome associated with lead exposure in adults by evaluating blood lead levels (>10 μg/dL) in Alabama adults (18 – 88 years of age) and their association with elevated incidence of cancers of the bladder, brain, kidney, lung, and/or stomach, these cancers found to be associated with lead by previous investigators. Based on studies indicating gene mutation/degradation and cancer development in animal models from lead exposure, we hypothesized that Alabama adults with documented elevated blood lead levels (BLLs) have a higher incidence of cancer than the overall Alabama population.[2]

We also studied whether elevated blood lead levels in adults are associated with increased mortalities from any cause, including deaths from major cancers, hypothesizing that adults with higher blood lead levels will have increased mortalities related to cardiovascular disease, kidney disease, and cancers.[6-9,12,21,22,27,34,41-43]

Our results are consistent with the literature and add to it, in light of our documented exposure levels and comprehensive follow-up of subjects for their cancer outcomes or deaths.

RETROSPECTIVE COHORT ANALYSIS ASSESSING LEAD EXPOSURE, CANCER INCIDENCE, AND ALL-CAUSE MORTALITY

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INTRODUCTION

The consequences for children with elevated blood lead levels (BLLs) are well established and include impaired cognitive development and ability, and damage to the nervous system even at levels below 5 µg/dL (IARC 2006; ATSDR 2007). Studies have also investigated the general health effects from lead exposure in adults. Health effects of concern include declining cognitive abilities, nerve damage, reproductive defects, cardiovascular illness, high blood pressure, stroke, cancer, and premature mortality (Jemal et al. 2002; Menke et al. 2006; ATSDR 2007; Schober et al. 2006). Despite lead being recognized as a harmful substance if ingested or inhaled, it is still unclear whether lead exposure contributes significantly to the burden of cancer. With the recent crisis in Flint, MI, it is now, more than ever, critical to understand the consequences of lead exposure (DeWitt 2017).

The National Toxicology Program (NTP) Report on Carcinogens, 14th Edition, classifies lead as "reasonably anticipated to be [a] human carcinogen" (NTP 2016). As of 2006, the International Agency for Research on Cancer (IARC) classified inorganic lead compounds as "probably carcinogenic to humans" and organic lead compounds as "not classifiable as to their carcinogenicity to humans." Epidemiologic studies reviewed by IARC have shown inconsistent results, ranging from weak associations with various cancers (especially lung, digestive, kidney, and brain cancers), to no associations or

protective associations; animal models demonstrated inconsistent positive associations (IARC 2006).

Evidence has shown that lead exposure is associated with DNA damage and prevention of DNA repair in rats and humans (IARC 2006). Disruption in DNA repair mechanism leads to malignant transformations and cancer development (Bhatti et al. 2009; Lubos et al. 2011; Torgovnick and Schumacher 2015; Wu et al. 2002). Therefore, it would not be unexpected to have elevated lead levels contribute to the development of various types of cancer (i.e., any cancer) and not just the specific organs targeted by lead in the blood.

However, as funding for state-based adult lead surveillance has decreased dramatically over the last decade, many unanswered questions are in danger of remaining unanswered.

To contribute to the body of knowledge, this retrospective cohort study evaluated lead exposure, cancer incidence, and all-cause mortality in Alabama's Adult Blood Lead Epidemiology and Surveillance (ABLES) cohort.

METHODS

Data sources

Lead exposure was assessed based on biological measurements of lead in the blood. Adults (18 – 88 years of age) whose blood lead levels were reported to the Alabama Department of Public Health (ADPH) as part of the ABLES program between 1990 and 2009 served as the cohort for this retrospective study.

ABLES is a state-based surveillance program, formerly funded by the Centers for Disease Control and Prevention (CDC). In Alabama, all lead laboratory results are mandated to be reported to ADPH (Williamson et al. 2014). Between 1990 and 2009, over 30 laboratories (including LabCorp, Quest Diagnostics, Southern Diagnostic, BioReference Laboratories, Mayo Medical Laboratories, and ARUP Laboratories) reported more than 50,000 lead test results (for Alabama residents 16 years and older) to ADPH. Adults may have been tested due to known high-risk occupations, symptoms of lead toxicity, and/or other non-occupational exposures. Employee screening for lead exposure is determined by industry. ABLES data represents all adults with reportable blood lead level results (limited to greater than or equal to 10µg/dL prior to 2008) regardless of reason or motivation for the testing.

The threshold at which blood lead levels are reportable to the State has been lowered throughout the years, but for the most part, electronic lab reporting had the greatest impact on the levels available in the dataset than the required level of BLL reporting. Prior to 2008, any BLL received over 10µg/dL was manually entered into the database, but once lab reports were received electronically and did not have to be keyed in, lower levels were stored, even before the lower levels became reportable in 2011.

Along with the measure of lead in the blood, demographic information like name, date of birth, and sex was also regularly reported; however, information regarding race, ethnicity, and whether exposure was work related was mostly missing.

CDC lists elevated blood lead levels as a nationally notifiable condition. In order to facilitate standard case description practices, CDC establishes case definitions for all notifiable conditions. The laboratory criteria within the case definition for elevated BLLs

decreased from 25 µg/dL to 10 µg/dL in 2009, and further decreased to 5 µg/dL in 2016, in response to recommendations by the Council of State and Territorial Epidemiologist's Position Statement 15-EH-01: Public Health Reporting and National Notification for Elevated Blood Lead Levels issued in 2015 (CSTE 2015). Because of this threshold for elevated BLLs being nationally recognized as 5 µg/dL and above, individuals with BLLs less than 5 µg/dL were used as the referent group.

Until funding ended, ADPH staff sent requests to the physician of record to obtain more complete demographic and contact information, but the surveys were infrequently returned. Of the 50,736 records in ABLES, 2,092 observations were excluded for laboratory testing of individuals less than 18 years of age or greater than 88 years of age. Individuals older than 88 years at the time of blood lead collection were excluded from this analysis (n=50) because the data for individuals greater than 88 years was sparse and, in some cases, questionable. Any duplicate patient records were merged so no BLLs were lost. The highest reported BLL for each individual was used to categorize exposure as the maximum level report to ADPH since more than a third of the individuals in the database had more than one BLL reported.

Cancer incidence data was gathered from the Alabama Statewide Cancer Registry (ASCR). The ASCR is a population-based registry that receives pathology reports and physician diagnoses since 1996 of primary cancers for individuals who are Alabama residents at the time of diagnosis or treatment (ADPH 2017). Cancer is also mandated to be reported to ADPH (ADPH 1995). The cancer registry collects name, date of birth, race, and information on cancer diagnosis. The North American Association of Central Cancer Registries (NAACCR) has awarded ASCR the highest level of certification (i.e.,

NAACCR Gold Certification) every year since 2004, which includes specific measures for at least 97% data completeness and ≥ 95% case ascertainment/representativeness (NAACCR 2018).

Mortality information for the ABLES cohort was obtained from the Alabama Center for Health Statistics (ACHS). All deaths for Alabama residents are required to be reported to ACHS. ICD-10 codes were obtained for the cause of death. Death certificates filed through December of 2017 were available for members of the ABLES cohort who died in Alabama. Information from the National Center for Health Statistics was not available because Social Security Numbers were not available for the ABLES cohort.

Analysis

Individuals in the ABLES database were linked to ASCR to assess cancer incidence outcome among members of the ABLES cohort. Reported cancer incidence through December 2017 was available. Data was compared by matching the individuals using CDC's Link Plus probabilistic record linkage. Individuals were matched by name, gender, and date of birth. Link Plus is part of the Registry Plus™ software provided by the CDC specifically developed for cancer registry data (HHS 2015). It mathematically assigns a score that represents the likelihood that the records are of the same individual while also diminishing the score if there is uncertainty about the match. The matching algorithm takes into account transposition of letters and numbers; common names versus less common names or spellings; and numerous other probabilistic matching

considerations. A threshold for matches was determined by manually reviewing all proposed record matches.

To calculate person years from BLL to cancer diagnosis or death, for individuals considered unexposed, the first reported BLL collection date was used. However, for individuals in exposure categories greater than or equal to 5 µg/dL, the date of the first BLL reported of at least 5 µg/dL was used. In the evaluation of time to cancer diagnosis, date of cancer diagnosis was used as the end date; if individuals were not censored due to a reported death, then the end time of December 31, 2017 was used. State-specific domestic outmigration rates for years prior to 2005 were not available in order to adjust the total cohort number to account for individuals who move out of the state in a given year for whom death information may not be received (Becher and Winkler 2017). Of the years available, the outmigration of individuals leaving Alabama only diminished the person years by 5-9 days per person year.

We assessed the cancer-related outcomes in adults with reported BLLs, specifically the incidence of bladder, brain, kidney, lung, and stomach cancer, as well as all-cause mortality. Although information about smoking status, past or present is not available in ABLES data, lung cancer is included in the analysis since smokers have been shown to have a higher lead levels attributable to the smoking (Cancer 2004; Hsu et al. 2009; Zareba et al. 1996).

The individuals in the <5 µg/dL exposure group within the ABLES cohort were used as the internal referent group. For the external comparison, ASCR provided age-sex- and race-specific cancer incidence rates for the overall Alabama population to be used as the external comparison group (Silva 1999).

Chi-square and Fisher's exact test were used to compare the unexposed group (BLLs <5 μg/dL) to the groups with 5 - <10 μg/dL, 10 - <25 μg/dL, and ≥25 μg/dL. These lead level groups are the same as those used by CDC's National Institute for Occupational Safety and Health (NIOSH). A classification of ≥40 μg/dL was added and the Cochran-Armitage test was used to evaluate for trends as the exposure category increased. Logistic regression compared exposure groups (≥10 μg/dL) to the control group while controlling for sex and 5-yr age groups. The exposure group with BLLs of 5 - <10 μg/dL were omitted from this dichotomous comparison to assure the actual BLL exposures did not overlap since CLIA regulations require laboratories to be accurate within 4 μg/dL(Parsons 1997). Measures of association with p-values <0.05 are considered statistically significant; 95% confidence limits were used.

Standardized incidence ratios (SIRs) and 95% confidence limits (CLs) were calculated by dividing the observed cancer incidence among the ABLES cohort by the expected cancer incidence in the Alabama population based on 5-year age groups by sex and race. Because of the small number of persons with race listed as not white or black, race was dichotomized as white and non-white. Crude incidence rates for all cancers as well as bladder, brain, kidney, lung, and stomach cancers for each age cohort were obtained from ASCR. Person years ended at the date of primary cancer diagnosis; if there was not a cancer diagnosis, time ended at date of death, if applicable, or December 31, 2017. Each individual's person years were further divided into their contribution to each 5-year age group, with no individual contributing more than five years per age group. By applying the 5-year age/sex/race incidence rates observed in Alabama 1996-2015 to the number of person years for exposed individuals in the same ABLES age-,

sex-, and race- cohort, we calculated the number of cancer cases expected for the ABLES exposed groups. The observed-to-expected ratio was used to produce SIRs, and the mid-P exact test was used to calculate 95% confidence intervals to measure precision, for each of the following exposure groups: ≥10 µg/dL, ≥25 µg/dL, and ≥40 µg/dL.

Similarly, standardized mortality ratios (SMRs) and 95% CLs were calculated by dividing the observed number of deaths among the ABLES cohort by the expected number of deaths in the Alabama population based on 5-year age group. Alabama's crude age-specific mortality rates from all causes, as well as deaths attributed to cancers, cardiovascular disease, and diseases of the nervous, respiratory, digestive, or genitourinary systems (ICD codes C00-D48, I00-I99, G00-G98, J00-J98, K00-K92, and N00-N98, respectively) were obtained from CDC's National Center for Health Statistics (which receives Alabama's mortality data from ACHS) via the Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER) tool. Person years ended at the date of death, or if there was not a date of death, on December 31, 2017. Each individual's person years were further divided into their contribution to each 5-year age group, with no individual contributing more than five years per age group. By applying the age-specific crude rates observed in Alabama 1999-2016 to the number of person years for exposed individuals in the ABLES cohort, we calculated the number of deaths expected for the ABLES exposed group. The observed-to-expected ratio is the SMR; 95% confidence interval was also calculated.

Because there were distinct race and sex differences between the ABLES cohort (62% of individuals with known race of non-white) and the Alabama adult population (~30% non-white), the 82% missingness of the race among the ABLES cohort could not

be ignored. Missingness at random (MAR) was verified in the data as there was a correlation of missingness where individuals were more likely to have missing race information in the categories with lower BLL exposure because individuals with higher BLLs were more likely to be investigated. A fully conditional specification multiple imputation model was used to fill in the nominal categorical variables of race and sex for calculating SIRs and SMRs.

RESULTS

Base Characteristics of the Cohort

After identifying and merging duplicate patient records and excluding any individuals with cancer diagnoses on the same date as, or prior to, the first BLL, 14,274 unique individuals remained in the ABLES cohort, of which 565 (4.0%) had a cancer

Table 1. Demographics and Characteristics of the Alabama ABLES Cohort 1990-2009

		Highest Lead Category Reported				
	Total	**<5 µg/dL**	**5-<10 µg/dL**	**10-<25 µg/dL**	**25 -<40 µg/dL**	**≥40 µg/dL**
No. of participants (% *row*)	**14,274 (100%)**	6,548 (45.9)	774 (5.4)	3,484 (24.4)	2,173 (15.2)	1,295 (9.1)
Total person-years	**177,224**	56,777	7,121	50,938	38,204	24,184
Mean age in years (SD)	**39.7 (14.4)**	43.2 (15.0)	42.6 (13.5)	38.2 (13.6)	34.5 (12.1)	33.5 (11.5)
Sex						
Male (%)	**12,147 (85.1)**	4,953	717	3,160	2,053	1,264
Female (%)	**1,732 (12.1)**	1,282	36	275	111	28
Missing (%)	**395 (2.8)**	313	21	49	9	3
Race						
White	**952**	32	17	329	342	232
Non-white	1,582	42	12	443	612	473
Missing/unknown	**11,740**	6,474	745	2,712	1,219	590
% Non-white among known race	62.4%	56.8%	41.4%	57.4%	64.2%	67.1%
Cancer diagnosis	**565**	223	27	166	79	70
Mean age in years of primary cancer diagnosis	**60.4**	61.8	60.7	59.4	61.5	56.8
Deaths	**1,178**	426	68	346	187	151
No. with single tests (%)	**8,995 (63.0)**	5,609 (85.7)	548 (70.8)	2,064 (59.2)	622 (28.6)	152 (11.7)

diagnosis and 1,178 (8.3%) died as of December 2017 (Table 1). Half of the cohort had peak blood lead levels less than 10 µg/dL, with 6,548 individuals serving as controls in the unexposed group (<5 µg/dL).

Cancer

The odds of developing any cancer was statistically significantly more in the three exposed groups with BLLs greater than or equal to 10 µg/dL, when compared with the internal comparison unexposed group (ORs 2.0, 2.1, and 3.7) when controlling for sex and age group (Table 2a). The odds of developing lung cancer was also higher in the exposed groups, compared with the unexposed group (ORs 3.2, 2.6, and 4.4). 'Any cancer' and lung cancer also both indicated a dose response relationship with increasing peak blood levels as indicated by the Cochran-Armitage trend test yielding p-values less than 0.5 (0.001 and 0.022, respectively). Incidence of bladder, brain, kidney and renal pelvis, and stomach cancer was too small in the ABLES cohort to detect significant associations or a trend.

Table 2a. Odds ratios and 95% Wald confidence intervals (CIs) for select cancer incidence among ABLES cohort, controlling for sex and age.

	Highest Lead Category Reported										Cochran-Armitage Trend Test
	<5 µg/dL		5-<10 µg/dL		10-<25 µg/dL		25 -<40 µg/dL		≥40 µg/dL		
	Obs	Ref	Obs	OR (95% CI)	Obs	OR (95% CI)	Obs	OR (95% CI)	Obs	OR (95% CI)	
Any cancer	223	1.0	27	1.1 (0.7, 1.6)	166	**2.0 (1.6, 2.5)**	79	**2.1 (1.6, 2.8)**	70	**3.7 (2.8, 5.0)**	**0.001**
Bladder	10	1.0	0	-	8	1.9 (0.7, 4.9)	5	2.5 (0.8, 7.7)	1	0.9 (0.1, 7.6)	0.738
Brain	4	1.0	1	1.9 (0.2, 17.4)	2	1.1 (0.2, 5.9)	0	-	2	3.5 (0.6, 20.4)	0.861
Kidney	6	1.0	3	**4.5 (1.1, 18.3)**	9	**3.7 (1.3, 10.8)**	2	1.6 (0.3, 8.0)	4	**5.8 (1.5, 21.9)**	0.136
Lung	33	1.0	5	1.4 (0.5, 3.5)	39	**3.2 (2.0, 5.2)**	14	**2.6 (1.4, 4.9)**	12	**4.4 (2.2, 8.7)**	**0.022**
Stomach	1	1.0	2	**18.1 (1.6, 203)**	3	9.3 (0.9, 90.1)	1	7.7 (0.5, 126.9)	0	-	0.695

Unexposed individuals were also compared with individuals with BLL ≥10 µg/dL collectively. Individuals with peak BLL greater than or equal to 10 µg/dL had more than twice the odds of developing cancer than the group whose BLL peaked below 5 µg/dL (Table 2b). Kidney and lung primary cancers were also statistically significantly associated with lead exposure, each with odds ratios greater than 3.0 (3.48 and 3.21, respectively).

Table 2b. Odds ratios and 95% Wald confidence intervals (CIs) for select cancer incidence among ABLES cohort, controlling for sex and age.

	Highest Lead Category Reported			
	<5 µg/dL		**≥10 µg/dL**	
	Obs	**Ref**	**Obs**	**OR (95% CI)**
Any cancer	223	1.0	315	**2.22 (1.8, 2.7)**
Bladder	10	1.0	14	1.92 (0.8, 4.5)
Brain	4	1.0	4	1.17 (0.3, 4.9)
Kidney	6	1.0	15	**3.48 (1.3, 9.6)**
Lung	33	1.0	65	**3.21 (2.1, 4.9)**
Stomach	1	1.0	4	5.75 (0.6, 52.1)

For the SIR, when the exposed groups (≥10 µg/dL) were compared with the external comparison group using person years as the denominator, 'any cancer' was statistically significant in each of the exposure levels (≥10 µg/dL, ≥25 µg/dL, and ≥40 µg/dL) but in a protective manner, with the observed number of cancer diagnoses in the ABLES cohort being 40% lower than that of the state's population (Table 3). The SIR for lung cancer in the exposure group with at least 25 µg/dL also showed a statistically significant deficit (SIR 0.7, CL 0.46, 0.99). SIRs for bladder, brain, kidney and renal pelvis, and stomach were not statistically significant.

Table 3. Standardized Incidence Ratios and 95% Confidence Limits (CLs) for Any Cancer and Selected Cancers for ABLES Cohort with Peak Blood Lead Level of at Least 10 µg/dL

Peak BLL	Person-years	Observed	Expected	SIR	95% CL
Any Cancers					
≥10 µg/dL	113,230	315	522	**0.6**	**(0.54, 0.67)**
≥25 µg/dL	62,376	149	266	**0.6**	**(0.47, 0.65)**
≥40 µg/dL	24,184	70	100	**0.7**	**(0.55, 0.88)**
Bladder					
≥10 µg/dL		14	16	0.8	(0.48, 1.40)
≥25 µg/dL		6	8	0.7	(0.30, 1.53)
≥40 µg/dL		1	3	0.3	(0.02, 1.63)
Brain					
≥10 µg/dL		4	7	0.6	(0.18, 1.35)
≥25 µg/dL		2	4	0.5	(0.09, 1.76)
≥40 µg/dL		2	1	1.4	(0.23, 4.62)
Kidney & renal pelvis					
≥10 µg/dL		15	18	0.8	(0.48, 1.34)
≥25 µg/dL		6	9	0.6	(0.26, 1.34)
≥40 µg/dL		4	4	1.1	(0.36, 2.75)
Lung					
≥10 µg/dL		65	77	0.8	(0.66, 1.08)
≥25 µg/dL		26	38	**0.7**	**(0.46, 0.99)**
≥40 µg/dL		12	14	0.8	(0.46, 1.44)
Stomach					
≥10 µg/dL		4	7	0.6	(0.19, 1.40)
≥25 µg/dL		1	3	0.3	(0.01, 1.42)
≥40 µg/dL		0	1	-	-

Mortality

Similarly, the SMRs did not identify any statistically significant positive associations, only protective, or inverse, associations (Table 4). Overall, each of the ABLES cohort exposures groups had fewer deaths than was expected of a group with similar age, race, and sex composition if the mortality rate had been that of the Alabama population. Mortality from any cause of death, analyzed due to their previous documented association with lead exposure, indicated that for each category assessed, there were statistically significantly fewer deaths than expected, ranging from 30 to 80% fewer deaths in the ABLES cohort.

Table 4. Standardized Mortality Ratios and 95% Confidence Limits (CLs) for All-cause Mortality and Selected Causes of Death for ABLES Cohort with Peak Blood Lead Level of at Least 10 µg/dL

Peak BLL	Person-years	Observed	Expected	SIR	95% CL
All-cause mortality (all ICD codes)					
≥10 µg/dL	114,607	684	1113	**0.6**	**(0.57, 0.66)**
≥25 µg/dL	63,013	338	571	**0.6**	**(0.53, 0.66)**
≥40 µg/dL	24,516	151	220	**0.7**	**(0.58, 0.80)**
Neoplasms (C00-D48)					
≥10 µg/dL		157	252	**0.6**	**(0.53, 0.73)**
≥25 µg/dL		78	127	**0.6**	**(0.49, 0.76)**
≥40 µg/dL		35	48	0.7	(0.52, 1.00)
Diseases of the nervous system (G00-G98)					
≥10 µg/dL		15	32	**0.5**	**(0.27, 0.76)**
≥25 µg/dL		7	16	**0.4**	**(0.19, 0.87)**
≥40 µg/dL		1	6	**0.2**	**(0.01, 0.82)**
Diseases of the circulatory system (I00-I99)					
≥10 µg/dL		238	368	**0.6**	**(0.57, 0.73)**
≥25 µg/dL		112	186	**0.6**	**(0.50, 0.72)**
≥40 µg/dL		51	72	**0.7**	**(0.53, 0.92)**
Diseases of the respiratory system (J00-J98)					
≥10 µg/dL		55	75	**0.7**	**(0.56, 0.95)**
≥25 µg/dL		28	36	0.8	(0.53, 1.11)
≥40 µg/dL		14	13	1.1	(0.61, 1.76)
Diseases of the digestive system (K00-K92)					
≥10 µg/dL		33	44	0.7	(0.52, 1.04)
≥25 µg/dL		13	23	**0.6**	**(0.31, 0.94)**
≥40 µg/dL		6	9	0.7	(0.27, 1.39)
Diseases of the genitourinary system (N00-N98)					
≥10 µg/dL		13	32	**0.4**	**(0.23, 0.68)**
≥25 µg/dL		7	16	**0.4**	**(0.19, 0.87)**
≥40 µg/dL		3	6	0.5	(0.13, 1.36)

DISCUSSION

When compared to individuals within the ABLES cohort with peak BLL below 5 µg/dL, a statistically significant positive trend of increased odds of any cancer, and also specifically lung cancer, was observed. Additionally, when comparing the unexposed to any exposure greater than 10 µg/dL, the odds of kidney or lung cancer were statistically significantly three times greater in the exposed group (3.48 and 3.21, respectively). These results are supportive of previous studies that also found an association between lead exposure and cancer incidence (Anttila et al. 1995; Chowdhury et al.; Englyst et al. 2001; IARC 2006; Lam et al. 2007; Lundström et al. 1997; NTP 2016; ATSDR 2007; Risch et al. 1988; Torgovnick and Schumacher 2015; Wu et al. 2002).

However, results varied significantly when using the internal versus the external comparison group. When comparing the cancer incidence and mortality rates of the individuals with elevated BLL within the ABLES cohort to the adults in the Alabama population, individuals within ABLES had fewer cancers and fewer deaths observed than were expected based on the age-, race-, and sex-specific calculations. These findings are not completely unexpected though since individuals within the ABLES cohort were most likely exposed through a work-related exposure and individuals who work in industries such as lead smelting or battery recycling, may be healthier than the general population at time of employment.

For the specific cancers that were reviewed, of bladder, brain, kidney, lung, and stomach, only lung cancer demonstrated a dose response relationship. Of the recent studies using BLLs as the measure of exposure, increased risk of lung cancer was identified in a variety of populations with elevated BLLs in Sweden, Finland, and the U.S. (Anttila et al. 1995; Chowdhury et al.; Englyst et al. 2001; Lam et al. 2007; Lundström et al. 1997). In a Finnish cohort study of 20,741 workers biologically monitored because of occupational exposure risks, the highest level of blood lead (collected 1973-1983) was linked to cancer incidence and mortality among; individuals with elevated BLLs were 1.8 times more likely to develop lung cancer (Anttila et al. 1995). Although several studies have previously mentioned a potential association between lead exposure and lung cancer, because smoking data was typically not available and a dose response correlation was not apparent, finding were downplayed. However, smoking has been shown to increase blood lead levels in smokers compared to

nonsmokers, and in this study, a dose response was evident (al-Saleh 1995; Brockhaus et al. 1983; Cancer 2004; Hsu et al. 2009; Zareba et al. 1996).

Several epidemiologic studies have investigated the general health effects from lead exposure. When the NHANES III data were assessed by Menke et al. for individuals over 20 years of age, no association between blood lead and cancer mortality was noted, though higher blood lead levels were significantly associated with overall deaths, cardiovascular diseases, myocardial infarctions, and stroke (HRs 1.25, 1.53, 1.78, and 1.59, respectively) (Menke et al. 2006). Yet, when Schober et al. reviewed the same dataset and limited it to individuals over 40 years of age, there was a significant association between elevated BLLs and deaths from all-causes, cardiovascular disease, and cancer, so perhaps the younger cohort (20-40 yrs. old) included in the other study diluted its results (Schober et al. 2006). This study, with a cohort with a mean age of 36.2 years in the exposed group, indicated a mortality was lower than expected among the exposed compared with the Alabama population as a whole.

In a 2014 retrospective cohort study, Chowdhury et al. assessed all-cause mortality for men having elevated BLLs in 11 ABLES states: California, Connecticut, Iowa, Massachusetts, Michigan, Minnesota, New Jersey, New York, Ohio, Pennsylvania, and Wisconsin. Men with BLL greater than 40 μg/dL had an increased standardized mortality ratio (SMR) for lung (1.20) and laryngeal (2.11) cancers. Risk of lung cancer mortality increased significantly as BLL increased. To date, that is the only study to identify an association of BLL with deaths from laryngeal cancer (Chowdhury et al.). Incidence of laryngeal cancer was reviewed during our analysis, but no association was found.

Strengths of this study include linkage and analysis of cancer incidence and blood lead levels in a previously unstudied population. Previous studies of the ABLES cohort did not include Alabama, or any state in the Southeast. The large cohort size and extended follow-up time enabled us to identify a dose-response relationship between lead exposure and incidence of lung cancer, and any cancer.

Limitations of our study include the lack of follow-up information for individuals in the ABLES cohort who may have moved out of state. In 2017, Becher and Winkler published calculations to account for outmigration adjustments, but the American Community Survey did not publish annual outmigration counts per state until 2005, so the calculations would have relied on too many assumptions for the years between 1990 and 2005 (Becher and Winkler 2017). Overestimates of the denominator may have resulted in slightly elevated person years for the cohort. Cancer cases and deaths may have missed for the same reasons. Additionally, exposures other than blood lead was not available for analysis.

Understanding long-term risks associated with adult lead exposure emphasizes that children are not the only population vulnerable to the adverse health outcomes from environmental lead exposure. More studies are needed to better understand the role lead plays in altering DNA to promote carcinogenesis.

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CONNECTING PUBLIC HEALTH SURVEILLANCE SYSTEMS TO INCREASE AWARENESS OF THE HEALTH EFFECTS RELATED TO HIGH LEAD EXPOSURE IN ADULTS

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INTRODUCTION

Adverse health effects and occupational risks associated with exposure to lead and lead compounds, are agreed upon (Cocco et al., 1997; DeWitt, 2017; IARC, 2006; Pesch et al., 2000; NTP, 2016; ATSDR, 2007; Steenland et al., 1992; Torgovnick and Schumacher, 2015; Wu et al., 2002). The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) have recommendations and regulations to protect employees from occupational exposure to lead (Administration; NIOSH; Perry, 2018). However, these thresholds do not imply that levels below the threshold are safe and studies continue to challenge whether there is any level of lead in the blood that is considered safe in children or adults (CSTE, 2015).

In 2006, Lam et al. published a study to evaluate the usefulness of linking in-state cancer registry reports to individuals reported to the state-based Adult Blood Lead Epidemiology and Surveillance System (ABLES) within New Jersey (Lam et al., 2007). In their cohort 3,165 men, individuals in the ABLES cohort were found to be 49% less likely to develop cancer than would have been expected in the overall New Jersey population (SIR = 0.51 with 95% CI 0.41, 0.62). Researchers suspected short follow-up times of fewer than 10 years and a 'healthy worker' effect may have contributed to this finding. However, although the healthy worker effect may influence all-cause mortality analysis in adults, the effect should be far less for cancer incidence, and according to Breslow and Day, may actually be negligible (Breslow, 1987).

ABLES is a state-based surveillance program, formerly funded by the Centers for Disease Control and Prevention (CDC). At the height of the program, in 2012 (prior to funding to states ending), 41 states were participating. Alabama has collected information on adults with elevated blood lead levels greater than or equal to 25 µg/dL since 1990. Like many public health surveillance systems, this information is usually stored in a surveillance database separate from other public health data systems that collect information related to outcomes. This study linked the information collected in ABLES with information collected in another separate public health data system, the Alabama Statewide Cancer Registry (ASCR).

The purpose of this study was to compare the findings of New Jersey's linkage study to Alabama's study using comparable ABLES and cancer registry data sources.

MATERIALS AND METHODS

Data Sources

Lead exposure was assessed based on biological measurements of lead in the blood. Adults (18 – 88 years of age) whose blood lead levels were reported to the Alabama Department of Public Health (ADPH) as part of the ABLES program between 1990 and 2009 served as the cohort for this retrospective study. To align with the New Jersey cohort, females were excluded, and only individuals with peak blood lead levels greater than or equal to 25 µg/dL were included.

In Alabama, all lead laboratory results greater than or equal to 25 µg/dL have been reportable to ADPH, since 1990 (Williamson et al., 2014). Between 1990 and 2009,

over 30 laboratories reported over 50,000 lead test results (for Alabama residents 16 years and older) to ADPH. Elevated blood lead levels in individuals less than 18 years old were investigated by another unit within ADPH so data on children 16-18 years old was not consistently captured; five individuals age 16-18 years old were excluded.

Adults may have been tested due to known high-risk occupations, symptoms of lead toxicity, and/or other non-occupational exposures. Employee screening for lead exposure is determined by industry. OSHA has regulations to protect employees against exposure to toxic and hazardous substances, including lead. OSHA field personnel visit work sites and test the air for lead and other chemicals from representative personal, work, and common areas at selected facilities. Individuals with a likely exposure to a lead air concentration of 50 $\mu g/m^3$ average per hour for at least 30 days must have their blood lead tested every six months (OSHA, 2006). Industries of concern include battery recycling and smelting, construction workers, and even firing range employees where dust from lead ammunition may be in the air. ABLES data represents all adults with reportable blood lead level results regardless of reason or motivation for the testing.

Along with the measure of lead in the blood, demographic information like name, date of birth, and sex was also regularly reported. Information regarding race, ethnicity, and whether exposure was work related was mostly missing. NIOSH analyzes lead exposure data submitted by states participating in ABLES. Of the adults with BLL ≥25 μg/dL, 82.8% included whether lead exposure was work-related. Of those where work-relatedness was reported, 93.7% were indeed work related (Alarcon, 2016; National Institute for Occupational Safety and Health (NIOSH) Division of Surveillance, 2018).

Cancer incidence data was gathered from the Alabama Statewide Cancer Registry (ASCR). The ASCR is a population-based registry that receives pathology reports and physician diagnoses since 1996 of primary cancers for individuals who are Alabama residents at the time of diagnosis or treatment (Health, 2017). Cancer is also mandated to be reported to Public Health (Health, 1995). The cancer registry collects name, date of birth, race, and information on cancer diagnosis. The North American Association of Central Cancer Registries (NAACCR) has awarded ASCR the highest level of certification (i.e., NAACCR Gold Certification) every year since 2004, which includes specific measures for at least 97% data completeness and ≥ 95% case ascertainment/representativeness (NAACCR, 2018).

Data sources for the New Jersey ABLES study have been previously described (Lam et al., 2007).

Analysis

Blood lead levels recorded in ABLES were assessed and unique individuals were identified. Any duplicate patient records were merged so no BLLs were lost. The highest reported BLL for each individual was used to categorize exposure as the maximum level report to ADPH.

ASCR provided age-specific cancer incidence rates for the overall Alabama population to be used as the comparison group for Alabama ABLES (Silva, 1999).

Individuals in the ABLES database were linked to ASCR to assess cancer incidence outcome among members of the ABLES cohort, and ACHS death certificates

to assess vital status. Reported cancer incidence and mortality through December 2017 were available. Data was compared by matching the individuals using CDC's Link Plus probabilistic record linkage. Individuals were matched by name, gender, and date of birth. Link Plus is part of the Registry Plus™ software provided by the CDC specifically developed for cancer registry data (U.S. Department of Health and Human Services, 2015). It mathematically assigns a score that represents the likelihood that the records are of the same individual while also diminishing the score if there is uncertainty about the match. The matching algorithm takes into account transposition of letters and numbers; common names versus less common names or spellings; and numerous other probabilistic matching considerations. A threshold for matches was determined by manually reviewing all proposed record matches.

To calculate person years from BLL to cancer diagnosis, the first BLL reported of at least 5 μg/dL was used. Date of cancer diagnosis was used as the end date; otherwise, if individuals were not censored due to a reported death, then the end time of December 31, 2017 was used. Alabama-specific domestic outmigration rates for years prior to 2005 were not available in order to adjust the total cohort number to account for individuals who move out of the state in a given year for whom death or cancer information may not be received (Becher and Winkler, 2017).

We assessed the cancer-related outcomes, specifically the incidence of brain, kidney, lung, and stomach cancer. These specific cancers had been associated with lead exposure in previous studies (Cocco et al., 1997; IARC, 2006; Pesch et al., 2000; NTP, 2016; ATSDR, 2007; Steenland et al., 1992). Additionally, because the previous study indicated a statistically significant inverse association for prostate cancer, prostate cancer

was included as well. Even though information about smoking status, past or present is not available in ABLES data, lung cancer will still be included in the analysis since smokers have been shown to have higher lead levels attributable to the smoking (IARC, 2004; Hsu et al., 2009; Zareba et al., 1996).

Standardized incidence ratios (SIRs) were calculated by dividing the observed cancer incidence among the Alabama ABLES cohort by the expected cancer incidence in the Alabama population based on 5-year age groups, race, and male sex. The crude incidence rates for all cancers as well as brain, kidney and renal pelvis, lung, prostate, and stomach cancers for each age cohort by race and sex were obtained from ASCR. By applying the age-, race-, and sex-specific incidence rates observed in Alabama 1996-2015 to the number of person years for exposed individuals in the ABLES age cohort, we calculated the number of cancer cases expected for the ABLES exposed group. Because the number of non-black, non-white men was few, races were categorized by rates associated with white and non-white races. The observed-to-expected ratio was used to produce the SIR. The Byar approximation to the exact Poisson test was used to calculate 95% confidence intervals for precision to mirror methods used in the original New Jersey study (Breslow, 1987). The mid-P exact test calculations did not yield significantly different results.

If a statistically significant excess of cancers is identified in the Alabama ABLES cohort, the full cohort (including those with peak BLL less than 25 µg/dL) will be assessed for a dose response relationship using the Mantel-Haenszel chi square test for a linear trend. Five exposure categories will be used: 0-<5, 5-<10, 10-<25, 25-<40, and ≥ 40 µg/dL.

Industry of the individuals within the ABLES cohort of men with BLL greater than or equal to 25 µg/dL will be reviewed and proportions assigned.

RESULTS

In Alabama ABLES, 31,138 BLL results represented 3,317 men whose highest blood lead level reported was greater than or equal to 25 µg/dL. Most of these males (78%) had more than one result reported, which is logical considering the industry requirements related to retesting employees at higher risk for lead exposure or with blood lead test result values of 40 µg/dL or higher.

Table 1. Comparison of characteristics of the men in the Alabama ABLES cohort and the New Jersey ABLES cohort

	Alabama ABLES	New Jersey ABLES[14]
No. of men	3,317	3,165
Total person-years	59,696	30,401
Years included	1990-2009	1985-2001
Mean follow-up time (in years)	18	10
Mean age in years of first BLL (range)	34 (18-85)	38 (15-92)
Cancer cases	142	83
Three most common cancer diagnoses (#)	Prostate (35)	Lung and bronchus (22)
	Lung and bronchus (26)	Prostate (16)
	Colon and rectum (17)	Colon and rectum (12)
Work-related industry type known	2,442 (73.6%)	3,156 (99.7%)

Table 1 provides a comparison of the Alabama ABLES cohort (1990-2009 to the New Jersey cohort 1985–2001). Although the number of males is similar in the two cohorts, the total person-years in the Alabama cohort is nearly twice that of the New Jersey cohort. Overall, the Alabama cohort appears to have been younger (34 years versus 38 years); however, because the standard deviation of the New Jersey cohort is not provided, we were unable to calculate 95% confidence intervals for each mean. Not

unexpected, with twice the person years, the Alabama ABLES cohort's cancer incidence is also nearly twice (i.e., 1.7 times) that of New Jersey's cohort.

Standardized incidence ratios

Table 2 shows the SIRs for the Alabama and New Jersey cohorts side by side with strikingly similar results, despite the Alabama cohort having almost twice as many person years of observation time. The Alabama and New Jersey ABLES cohorts both demonstrated observed cancer incidence overall that was 50% less than expected when compared to the overall population of the state. Additionally, the Alabama cohort also showed a statistically significant deficit of lung and bronchus cancers (SIR = 0.5, 95% CI 0.36, 0.80) and stomach cancers (SIR = 0.2, 95% CI 0.00, 0.96) compared with the state's population.

Table 2. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for cancer incidence among males in Alabama and New Jersey ABLES with BLL ≥25 µg/dL compared with each state's population

	Alabama† 59,862 person-years			New Jersey‡ 30,401 person-years		
	Exp	Obs	SIR (95% CI)	Exp	Obs	SIR (95% CI)
All types	282.4	142	**0.5 (0.43, 0.59)**	162.3	83	**0.5 (0.41, 0.62)**
Brain	3.4	2	0.6 (0.07, 2.12)	2.4	2	0.8 (0.09, 3.00)
Kidney and renal pelvis	11.7	6	0.5 (0.19, 1.12)	5.4	5	0.9 (0.30, 2.17)
Lung and bronchus	47.8	26	**0.5 (0.36, 0.80)**	24.3	22	0.9 (0.57, 1.37)
Prostate	83.8	35	**0.4 (0.29, 0.58)**	45.3	16	**0.4 (0.20, 0.57)**
Stomach	5.8	1	**0.2 (0.00, 0.96)**	3.6	4	1.1 (0.30, 2.82)

† - Alabama ABLES cohort 1990-2009, observed cancer incidence through 2017

‡ - New Jersey cohort 1985-2001, observed cancer incidence through 2001

Linear trend

The follow-up test for linearity across the BLL exposure groups within the ABLES cohort resulted in a statistically significant positive trend for any cancer diagnosis (p-value = 0.001) as the peak exposure of the individuals increased from no exposure (0-<5 µg/dL) to the highest level of BLL categorized (≥40 µg/dL). A linear trend was not observed for lung or prostate cancer, though lung cancer was close, at p-value just outside the threshold for 95% confidence (p-value 0.065). (Table 3)

Table 3. Extended Mantel-Haenszel chi square for linear trend in full male Alabama ABLES cohort (1990-2009) for all types of cancer and selected cancers.

	Lead Exposure Level (µg/dL)					M-H χ^2 for Linear Trend p-value
	<5 n = 4,953	5-<10 n = 717	10-<25 n = 3,160	25 -<40 n = 2,053	≥40 n = 1,264	
All types	156	22	150	73	69	**0.001**
Lung Cancer	21	4	37	14	12	0.065
Prostate Cancer	51	4	32	21	14	0.740

Industries

In the Alabama ABLES cohort, standard industrial classification (SIC) codes were sparse with only 50.0 % of those with BLL greater than or equal to 25 µg/dL containing that level of employment information, and only 7.6% of the individuals with BLL less than 25 µg/dL with a SIC code, unlike 99.7% of the New Jersey ABLES cohort that contained this information. The Alabama ABLES cohort was more likely to have the North American Industry Classification System (NAICS) code complete (74.1%). In New Jersey ABLES cohort with BLLs greater than or equal to 25 µg/dL, 75% worked in manufacturing. However, the men in the Alabama ABLES cohort with elevated BLLS whose record contained a SIC code, 62% worked in either secondary smelting and

refining of non-ferrous metal, or rolling drawing, and extruding of non-ferrous metals. Lead is a non-ferrous metal.

DISCUSSION

Limitations

Limitations of this study were similar to those noted in the New Jersey study, specifically limitations not uncommon for retrospective cohorts where you are limited to the information collected in the past and currently available. Alabama ABLES data was also missing the race information for most of the individuals, although required as part of the demographics to be included with the report of the BLL (Williamson et al., 2014). Cancer incidence, especially prostate and lung, varies greatly among the races. Although Alabama and New Jersey have a similar percent of white residents (69.2% and 72.1%, respectively) according to the U.S. Census population estimates for July 2017, their percentages of black and Asian residents varies (26.8% vs. 15.0%, and 1.5% vs 10.1%, respectively). That being said, inferences cannot be made as to the makeup of the ABLES cohort within each state, but understanding it may be at least as different as the states' overall populations. After verifying the race information was missing at random and was correlated with the peak BLL of the individual, multiple imputations was used to impute the race data so age-, race-, and sex-specific crude rates could be used to calculate the SIR.

Additionally, because lead exposure is not common in the United States population outside of occupational exposure, it is difficult to assess the proportion of

cancers that are attributable to lead when most of these industries that are at high-risk of lead exposure are also at risk for exposure to a variety of other chemicals or metals that are known or suspected carcinogens.. It is also plausible that with occupational regulations and safety measures in place, that a peak BLL could be less indicative of long-term exposure risk and more indicative of measures in place to ensure reduced risk for employees, and thus a lower risk of cancer.

Epidemiologic studies

Considering the dose response trend within the ABLES cohort, the findings of this report are consistent with other studies that have noted increased risk of cancers associated with occupational lead exposure. Of the recent studies using BLLs as the measure of exposure, increased risk of lung cancer was identified in a variety of populations with elevated BLLs in Sweden, Finland, and the U.S. (Anttila et al., 1995; Chowdhury et al.; Englyst et al., 2001; Lam et al., 2007; Lundström et al., 1997). In a Finnish cohort study, the highest level of blood lead (collected 1973-83) was linked to cancer incidence and mortality among 20,741 workers biologically monitored because of occupational exposure risks (Anttila et al., 1995). Individuals with elevated BLLs were 1.8 times more likely to develop lung cancer. Although several studies have mentioned a potential association between lead exposure and lung cancer, smoking data was not available and a dose response correlation was not apparent. Although information about smoking status, past or present was not available in Alabama ABLES data, lung cancer was included and is still relevant because smokers have been shown to have a higher lead

levels attributable to the smoking in previous studies comparing lead levels of smokers and nonsmokers (al-Saleh, 1995; Brockhaus et al., 1983; IARC, 2004).

Conclusions

Collectively, lead exposure risks for adults in the Southeast specifically, have not been previously studied. Each of the previous studies using ABLES data did not include data from adults in the Southeastern United States. Additionally, the more recent study of 11 states (CA, CT, IA, MA, MI, MN, NJ, NY, OH, PA, WI) showed statistically significant elevated standardized mortality ratios for lung cancer (Chowdhury et al.). It is important to understand outcomes associated with occupational lead exposure since occupations related to lead recycling will continue as long as we remain dependent on batteries with lead plates. Almost half of the states with commercial battery recycling plants (AL, CA, FL, IN, MN, MO, NY, PA, SC, and TX) are in the South (Association of Battery Recyclers, 2018).

The findings of this study, despite its limitations, indicate that those tested for lead exposure may have fewer cancer than the overall population, although potential outmigration may have also resulted in a slight overestimation of person years, or underreported events in the cohort. These results are almost identical to the results using the New Jersey cohort more than ten years ago. Even with the limitations of each study, it is thought provoking and hypothesis generating.

Not unlike the body of evidence with seemingly conflicting results, within the cohort, there is a dose response trend indicating individuals with higher peak BLLs are at an increased risk of cancer than those within the cohort with limited exposure to lead.

Results from this study support the need for continued state surveillance, enabling public health to provide appropriate recommendations to prevent adverse health effects. Each state could contribute to this body of knowledge by linking the data within their own public health surveillance systems. A better understanding of the long-term risks associated with lead exposure and the benefits of employee screening programs could impact OSHA lead exposure regulations in the future.

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DISCUSSION

Within the ABLES cohort, individuals in the three highest exposure groups (10-<25, 25 -<40, and ≥40 µg/dL) had significantly increased odds of developing cancer of any type (ORs 2.0, 2.1, and 3.7, respectively) compared with the internal referent group with the lowest BLLs (<5 µg/dL). These results are supported by the research that shows how lead is associated with DNA damage and disruption of DNA repair. Disruption in DNA repair mechanism leads to malignant transformations and cancer development. The three highest exposure groups also had statistically significant increased odds of lung cancer (ORs 3.2, 2.6, and 4.4, respectively). Although smoking is a known cause of lung cancer and smoking status was not available, there is no reason to believe individuals with higher BLLs in the ABLES cohort would be more likely to smoke than individuals in the ABLES cohort with low BLLs. Lead is also a component of cigarette smoke, so individuals who smoke or are exposed to second-hand smoke have higher BLLs attributable, in part, to the smoking.[30,44-47] National ABLES data indicates that of persons with ≥25 µg/dL for whom exposure is reported, 94% are work related.[48] A positive dose response within the cohort is apparent for 'any cancer' and lung cancer (p-values 0.001 and 0.022); as the lead exposure as indicated by the BLL, the risk of these two categories of cancer also increased across the five exposure categories.

Lead exposure has also been associated with kidney diseases and this study indicated that individuals in four higher exposure categories had an increased odds of kidney cancer when compared to the lowest exposure group (ORs 4.5, 3.7, 1.6, and 5.8) , though the 25 -<40 µg/dL category had few cases and did not reach statistical significance.

When individuals with BLL ≥10 µg/dL were compared to the low exposure group (<5 µg/dL), 'any cancer', lung, kidney, brain, bladder, and stomach were suggestive of an elevated risk, with 'any cancer', lung, and kidney each achieving statistical significance.

However, when using the Alabama population as an external comparison group, exposed persons in the full ABLES cohort had a statistically significantly decreased odds of cancer, as did the men in the highest exposure categories (≥25 µg/dL) in New Jersey's study, potentially supporting the theory of a healthy worker effect; although, loss to follow-up may have also contributed to this difference.[29] Individuals hired into occupations with lead exposure risk, like battery recycling, construction, or manufacturing of lead products, may be healthier than the overall adult Alabama population prior to employment. The dose response identified within the cohort would not be influenced by any differences between the ABLES cohort and the overall state adult population.

Strengths of this study include the detection of a significant dose response in the full adult ABLES cohort, as well as for the men with the highest BLL recorded as ≥25 µg/dL, indicating that with higher BLLs there is an increased risk of cancer in adults. Using BLLs to measure exposure is both a strength and a limitation. The value of the

BLL is that at some point in time, individuals in the higher exposure categories were exposed to unsafe lead levels. However, without serial BLLs per person or exposure details, such as occupation, it is unclear if the individual's exposure was long term, or at a single point in time since 63% of the individuals had only a single BLL result.

The linkage to two other public health databases is invaluable as the information could be associated for a more comprehensive view of exposure and outcome for these individuals, spanning an average of 12.4 years of follow-up time per person, assuming that the individual did not move out of state during the study time. The data from the cancer registry and mortality information through 2017 allowed for time after the last recorded lead exposure in 2009 for cancer or long-term health effects to occur. It is reasonable to assume a proportion of the ABLES cohort left Alabama prior to the end of the study. Adjustments published by Becher and Winkler to account for incomplete follow-up data depends on known annual outmigration rates, unavailable prior to 2005. For the overall Alabama population, between 2005 and 2016, according to the American Community Survey, the rate of individuals leaving Alabama ranged between 20.8 and 24.2 per 1,000 persons each year which is approximately 7 to 9 days per person year. Wee cannot speculate how these outmigration statistics apply to the adults within the ABLES cohort, whether they would be more or less likely to stay in the state. However, there is no indication that the individuals who leave the state would be more or less likely to have one of the outcomes of interest in this study.

The comparison to the New Jersey linkage study yielded strikingly similar results, corroborating the findings of each with reproducibility.

The individuals in ABLES are the result of targeted testing based on the identification of known or suspected risk factors in adults. This information is not used to infer incidence or prevalence of the overall population but is used as a data source for identifying additional risk factors within the at-risk population, and cancer and mortality outcomes associated with elevated levels. Universal or random testing would not be practical since most of the population is not at risk for lead exposure. ABLES contains information on Alabamians with known elevated BLLs as a result of mandates requiring all physicians, nurses, and laboratory directors to report.

These results are not generalizable to the population outside the ABLES cohort. Adults in the ABLES cohort are part of targeted passive surveillance. These individuals are tested for reasons of suspected lead toxicity, suspected exposure through their occupation or hobbies, or known high-risk occupations. As is a caveat with most retrospective cohort analyses, information pertaining to other carcinogenic exposures is unknown.

ASCR, with its NAACCR Gold Certification, contains primary cancer diagnoses for individuals who are treated or diagnosed in Alabama. The ASCR may also receive notifications from other states if the patient has Alabama listed as their state of residence. If an individual lived in Alabama at the time their BLL was drawn, but moved out of state afterward, and was diagnosed with cancer in another state, ASCR would likely not have any record of that diagnosis. The cancer rates in the ABLES cohort will therefore be a slight underestimate. Similarly, deaths are reported based on the person's state of residence at the time of death. For this reason, deaths among the ABLES cohort may also

be an underestimate of mortality since only deaths that occur in Alabama would be reported to ACHS.

Conclusions

In summary, individuals within the ABLES cohort with elevated BLLs (≥10 µg/dL) indicating lead exposure have an increased odds of any cancer, kidney and renal pelvis cancers, and lung cancer compared to referent group with BLLs <5 µg/dL. Individuals within the ABLES cohort may be healthier than the overall adult population of Alabama as a healthy worker effect, apparent when calculating SIRs and SMRs using the Alabama population to calculate expected numbers of cancers and deaths for the cohort, although potential outmigration may have also resulted in a slight overestimation of person years, or underreported events in the cohort.

Results from this study support the need for continued state surveillance, enabling public health to provide appropriate recommendations to prevent adverse health effects. Although these findings are not generalizable to the population, understanding specific risks to a specific population of concern, such as the ABLES cohort, facilitates targeted prevention messages to improve overall public health.

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