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Low-Dose Radiation Risks of Lymphohematopoietic Cancer Mortality in U.S. Shipyard Workers

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The linear, non-threshold (LNT) hypothesis of cancer induction derived from studies of populations exposed to moderate-to-high acute radiation doses may not be indicative of cancer risks associated with lifetime radiation exposures less than 100 mSv. The objective of this study was to examine risks and dose-response patterns of lymphohematopoietic cancer (LHC) and its types associated with low radiation exposure while adjusting for possible confounding factors. A retrospective cohort of 437,937 U.S. nuclear shipyard workers (153,930 radiation and 284,007 non-radiation workers) was followed from 1957 to 2011, with 3,699 LHC deaths observed. The risk of LHC in radiation workers was initially compared to the risk in non-radiation workers. Time dependent accumulated radiation dose, lagged 2 years, was used in categorical and continuous dose analysis among radiation workers to examine the LHC risks and possible dose-response relationships based on Poisson regression models. These analyses controlled for sex, race, time dependent age, calendar time, socioeconomic status, solvent-related last job, and age at first hire. The median lifetime radiation dose for the radiation worker population was 0.82 mSv and the 95th percentile dose was 83.63 mSv. The study shows: 1. LHC mortality for radiation workers was significantly lower than non-radiation workers relative risk: 0.927; 95% confidence intervals (95% CI): 0.865, 0.992; P = 0.030]. Among LHC types, the risks for lymphoid leukemia and lymphomas in radiation workers were lower than the risk in non-radiation workers with statistical significance, while the risk for the rest of LHC types did not show any statistically significant difference. 2. In categorical dose analysis among radiation workers, sample size weighted linear trend of relative risk (RRs) for LHC and its types in five dose categories (>0–<25, 25–<50, 50–<100, 100–<200, and > = 200 mSv) vs. 0 mSv were not statistically significant, although there was an elevation of RR for chronic myeloid leukemia only in the 50-<100 mSv category (RR: 2.746; 95% CI: 1.002, 7.521; P = 0.049) vs. 0 mSv. 3. The Poisson regression analyses among radiation workers using the time dependent radiation dose as a continuous variable showed an excess relative risk (ERR) for LHC at 100 mSv of 0.094 (95% CI: –0.037, 0.225; P = 0.158) and leukemia less chronic lymphoid leukemia, of 0.178 (95% CI: –0.085, 0.440; P = 0.440) vs. 0 mSv. The ERRs and their linear trend for all other types were not statistically significant.

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INTRODUCTION

The common lymphohematopoietic cancers (LHCs) and diseases seen in the scientific literature are leukemia; leukemia, excluding chronic lymphoid leukemia (leukemia less CLL); multiple myeloma; Hodgkin's/non-Hodgkin's lymphoma; myeloproliferative neoplasms and myelodysplastic syndrome. Of these, leukemia less CLL is one of the most reported LHC types in published studies on radiation risk among radiation workers and primarily consists of myeloid cell cancers (*1–12*). When evaluating the mortality risk to leukemia, all types and combinations are important to consider.

Radiation protection standards have relied heavily on radiation risk models derived from populations exposed to moderate-to-high, acute radiation exposure (*7, 8, 13, 14*). Because of concerns that cancer risks calculated using these patterns and levels of exposure may not be indicative of the cancer risks associated with occupational radiation workers, the focus of recent research has shifted from examining the risks associated with moderate-to-high, acute radiation exposure to those of repeated low-dose, chronic exposures (*1, 4, 8–10, 15–20*). These studies evaluating the risk of low-dose chronic exposures have evaluated radiation workers from a variety of fields, such as industrial, nuclear, environmental, and medical. In 2011, Daniels and Schu-

bauer-Berigan (*21*) reviewed 23 independent studies and concluded that protracted exposure to low-dose radiation was significantly associated with the risk of leukemia based on the aggregated relative risk (RR). Many of the studies included in this meta-analysis did not show any statistical significance by themselves, which in many cases was due to small cohort size or short follow-up periods. Among these studies, the largest one was a 15-country collaborative study of cancer risk among radiation workers in the nuclear industry (*1, 2*). Cardis et al. (*1*) reported an excess relative risk (ERR) for leukemia less CLL of 1.93/Sv (90% CI $<$ 0.00, 8.47); however, this result failed to reach statistical significance. Since then, several other larger studies have been published. The ERR for leukemia less CLL was 1.7/Sv (95% CI: 0.22, 4.70) when lagged for 7 years in radiation-monitored personnel from the United States pooled radiation workers used in the International Nuclear Workers Study (INWORKS) (*18*). For leukemia, under a simple linear model, the ERR per Gy was 2.75 (90% CI 1.73; 4.21) in the Life Span Study (LSS) and 3.15 (90% CI: 1.12, 5.72) in INWORKS, with evidence of curvature in the association across the range of dose observed in the LSS but not in INWORKS (*8*). Several studies have used Poisson linear ERR models for radiation and cancer research and the underlying dose-response curves for LHC, especially leukemia, were assumed to be linear (*1, 8, 9, 18, 22–24*). However, some other studies suggest the dose-response curves for leukemia are linear quadratic (*13, 24*).

In 1991, Matanoski et al. evaluated the risks of LHC and leukemia deaths among male U.S. nuclear shipyard workers involved in nuclear-powered ship overhauls with a 24-year follow-up period (1957–1981) based on a stratified random sampling frame (*4*). The primary source of radiation exposure to these workers was high energy photons (i.e., $>$400 keV, mainly Co-60) emitted by activated corrosion products deposited within reactor plant piping systems. Most radiation exposure to shipyard personnel came from activities associated with the inspection, maintenance, and repair of these piping systems (*4*). Although the standardized mortality ratio (SMR) analyses comparing radiation and non-radiation workers to U.S. white males (white males were used as the comparison population due to the lack of race data in some shipyard records) indicated no statistically significant excess risk for LHCs, an internal analysis showed that shipyard workers who received greater than 50.0 mSv lifetime exposure had RRs of 2.41 (95% CI 0.5, 23.8) and 2.94 (95% CI 1.0, 12.0) for leukemia and all forms of LHCs, respectively, relative to workers with lifetime occupational doses between 5.0 and 9.99 mSv (*4*). However, when non-radiation workers were compared to the same exposed control group, non-radiation workers showed RRs of 2.37 (95% CI 0.6, 20.5) and 3.58 (95% CI 1.3, 13.5) for leukemia and all forms of LHCs, respectively. The similarity in the results between the greater than 50.0 mSv lifetime exposure group and the non-radiation worker group suggest that these results do not definitively show an excess risk of cancer in the greater than 50.0 mSv group, but more likely that there was something unique with the control group (i.e., $\geq$5.0–9.99 mSv) chosen for comparison (*4*). More studies were needed to explore the risk of LHC for this shipyard worker cohort.

For low doses, the dose-response paradigm is based on radiation risk estimated by extrapolation of high-dose data. The International Commission on Radiological Protection (ICRP) (*25*) has concluded that, while existence of a low-dose threshold seems likely for radiation-related cancers of certain tissues, the evidence does not favor the existence of a universal threshold. The linear, non-threshold (LNT) hypothesis remains a prudent basis for radiation protection at low doses and low dose rates (*25, 26*). Many recent biological studies have indicated a so-called ''hormesis'' effect, a beneficial effect caused by biological adaptive responses such as increases in immunity, antioxidants, DNA repair, cell cycle arrest, apoptosis, and senescence from low doses of radiation (*27–31*).

The present research was to expand the above shipyard worker cohort by 1. covering a study period from 1957 to 2011, 54 years total follow-up, and 2. covering all shipyard workers employed from 1957 to 2004 rather than a sampled subset as in the previous study (*4*). This would involve a new death search for all shipyard workers unless their vital status was known to be deceased in the original study. An updated standardized mortality ratio (SMR) evaluation of disease risks of shipyard workers exposed to low dose ionizing radiation on this newly expanded cohort was published (*32*). The result showed that SMRs for both radiation and non-radiation workers had lower risks of death from all causes [0.74; 95% confidence interval (CI) 0.74 to 0.75 and 0.77; 95% Cl 0.77 to 0.78, respectively] and from all cancers (0.92; 95% CI 0.91 to 0.93 and 0.90; 95% CI 0.89 to 0.91, respectively) compared with U.S. white males. Asbestos-related diseases including pleural cancers, mesothelioma, and asbestosis, but not lung cancers, were statistically higher in both radiation and non-radiation workers compared with the U.S. white males. The objective of this study was to examine general mortality risks in all U.S. nuclear shipyard radiation workers for LHC and its types using multivariate Poisson regression analysis and controlling for sex, race, calendar time, and time-dependent age. Lag periods were also incorporated into the analyses to determine if any LHC type exhibited latent effects. Overall, the results of this study will be used to determine which LHC types show increased mortality risk to low-dose radiation exposure and would be good candidates for a more detailed evaluation controlling for an even more stringent set of confounders (solvent exposure, socioeconomic status, etc.) and lag periods specific to that LHC type. Most importantly, the shape of dose-response relationship at low radiation doses will be examined and discussed.

TABLE 1
Lymphohematopoietic Cancer (LHC) Grouping

Cancer sites	ICD codes version 9	ICD codes version 10
LHC	200–208, 238.4, 238.7, 273.3.	C81–C96, D45–47
Leukemia	204-208 excl. MNM	C91–C95 excl. MNM
All leukemia less CLL	Leukemia excl. CLL	
Lymphoid leukemia (LL)	204	C91
Acute lymphoid leukemia (ALL)	204.0	C91.0
Chronic lymphoid leukemia (CLL)	204.1–204.2	C91.1, C91.2
Other lymphoid leukemia (OLL)	Lymphoid leukemia except for ALL and CLL	
Myeloid leukemia (ML)	205	C92
Acute myeloid leukemia (AML)	205.0	C92.0, C92.4–C92.6
Chronic myeloid leukemia (CML)	205.1–205.2	C92.1–C92.2
Other myeloid leukemia (OML)	ML except for AML and CML	
Other leukemia (OL)	Leukemia except for LL and ML	
Multiple myeloma (MM)	203.0, 203.1	C90.0–C90.3
Lymphomas	200, 201, 202, 273.3	C81–86, C88.0-C88.4, C96
Hodgkin's lymphoma (HL)	201	C81
Non-Hodgkin's lymphoma (NHL)	200, 202, 273.3	C82–86, C88.0–C88.4, C96
Myeloproliferative neoplasms and myelodysplasias (MNM)	238.4, 238.7	C94.4, C94.6, C88.8, D45–47

METHODS

Data Collection

Data for this study were collected from multiple sources over a period of time. This section describes the data acquired from various data sources.

Cohort Population

The study population consisted of 440,892 workers at eight (six public and two private) shipyards conducting overhauls of nuclear-powered vessels: Charleston Naval Shipyard, Charleston, South Carolina; General Dynamics Corporation, Electric Boat Division, Groton Connecticut; Mare Island Naval Shipyard, Vallejo, California; Newport News Shipbuilding and Drydock Company, Newport News, Virginia; Norfolk Naval Shipyard, Norfolk, Virginia; Pearl Harbor Naval Shipyard, Pearl Harbor, Hawaii; Portsmouth Naval Shipyard, Portsmouth, New Hampshire; and Puget Sound Naval Shipyard, Bremerton, Washington. At the public shipyards, workers were identified either from personnel records, Form W2 lists, and/or from Office of Personnel Management records for the period 1957 through 2004. For the two private shipyards, the workers were identified from hard-copy or computerized personnel records for the same period. Overall, 2,955 workers (0.7%) were excluded because they were lacking critical information such as gender or social security number. The final number of workers included in the study cohort was 437,937.

Although the Navy's occupational monitoring program began in the 1940s, the cohort follow-up period began in 1957, as this was the beginning of nuclear-powered ship overhauls and significant radiation exposure in shipyard radiation workers. For all radiation workers included in the follow-up, who had exposure prior to 1957, their prior dose was provided for inclusion in the study.

All 437,937 workers, including workers initially employed from 1957 to 1981 in the original study (*4*), workers employed from 1957 to 1981 but not in the original study sample, and all subsequent employees newly-hired from 1981 through 2004, were followed up for deaths from January 1, 1957 to December 31, 2011. Because non-radiation workers were required to have had at least one year of employment to be eligible for inclusion in the study, their follow-up start dates were one year following their hire date or January 1, 1957, for those employed more than one year prior to 1957, whichever was later. There was no one-year-employment requirement for radiation workers since all had previous non-radiation employment; thus, their follow-up start date was the first date of radiation work or January 1, 1957, whichever was later. For each worker, the follow-up ended on the date of death or December 31, 2011, whichever was earlier. In this case, their follow-up started when they became a radiation worker; the employment duration prior to their radiation job was counted in their total employment duration, but not included in their follow-up period, the period during which the deaths were collected. The radiation dose-response analysis was done on radiation workers only, using those workers who have 0 mSv time dependent occupational radiation dose as the reference group, in addition to radiation vs. non-radiation workers comparison.

Collection of Death Data

In the original cohort enrolled through 1981, all sampled workers were followed for vital status (alive, dead, or unknown) through records of the U.S. Social Security Administration, the U.S. Civil Service, the U.S. Health Care Financing Administration, and the Veteran's Benefits Administration, as well as through mortality data from some states and the eight shipyards (*4*). Causes of death were determined from reviewing and coding of death certificates by the study nosologist. For the expanded study, additional death information through 2011 for all workers in the original cohort who were still living in 1981, all workers employed from 1957 to 1981 but not in the sample of the original study, and all subsequent employees newly hired from 1981 through 2004 was obtained from four sources: the National Death Index, Social Security Administration mortality records, a private organization called Pension Benefits Information, and state mortality databases. Causes of death were coded according to the International Classification of Diseases (ICD) 9th or 10th Revision depending on the year of death. The primary causes of deaths were used in this study.

LHC Grouping

LHC and its types were classified based on ICD coding of deaths using modified grouping criteria from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program categories (*33*) as shown in Table 1. LHC and its types including lymphoid leukemia (acute, chronic, and other), myeloid leukemia (acute, chronic, and other), and leukemia other than lymphoid or myeloid type, multiple myeloma, lymphomas, and a type of myeloproliferative neoplasms and myelodysplasias were examined separately. Analyses of LHC

TABLE 2
General Information of the Shipyard Cohort Follow Up by Radiation Group

Variables	Non-radiation workers	Radiation workers	Total
Number of workers followed	284,007	153,930	437,937
Number of male workers followed	227,292	149,527	376,819
Number of female workers followed	56,715	4,403	61,118
Follow-up period	1957-2011	1957-2011	1957-2011
Years of employment	10.8	19.4	13.8
Years of employment for radiation jobs	0.0	9.3	
Average follow up years	29.9	31.8	30.6
Total follow up person-years†	8,499,273	4,894,126	13,393,399
Total male follow up person-years†	6,740,241	4,793,345	11,533,586
Total female follow up person-years†	1,759,032	100,782	1,859,813
Total time-dependent person-years	8,357,107	4,817,211	13,174,318
Median lifetime occupational radiation dose‡	0	0.82 mSv	
75th percentile lifetime occupational radiation dose‡	0	10.71 mSv	
95th percentile lifetime occupational radiation dose‡	0	83.63 mSv	
Average lifetime occupational radiation dose‡	0	15.36 mSv	
Total deaths observed	87,325	51,587	138,912
Male deaths observed	77,975	51,346	129,321
Female death observed	9,350	241	9,591
Total mortality (1/100,000 person-years)	1,027	1,054	1,037

† Follow up period is the period in which the deaths have been collected.
‡ 1 Millisievert (mSv) = 100 millirem (MREM) = 0.1 rem (REM).

types were undertaken to identify the specific LHCs that are associated with low-dose, chronic radiation exposure. The current study has included leukemia less CLL as an LHC type in analyses for comparison to other studies.

Radiation Worker Selection and Exposure History

For this study, the radiation worker population were personnel engaged in shipyard work that could have resulted in potential exposure to radiation and therefore required special training and dosimetry, in contrast to, the non-radiation worker population. The non-radiation worker population were employed by one of the shipyards but did not perform any radiation specific work. Radiation workers were individually monitored by one of three dosimetry systems, comprised of either film or thermoluminescent dosimeters, since the onset of the Navy's dosimetry program, which began in the 1940's. A typical dosimetry issue period in the shipyards was weekly, but other issue periods were used based on need, dosimetry processing cycle or job. Regardless, of the issue period, all dose was background corrected, using background dosimeters, and used to determine the cumulative annual occupational dose to the worker. It is these annual occupational doses that were supplied for each radiation worker in the population. For those shipyard workers that had dose prior to 1957, all exposure information dating back to the origin of the program in the 1940s was included. Radiation doses used in analyses were time-dependent cumulative doses for each year of follow-up. Thus, all radiation doses prior to 1957 were added to the annual cumulative doses for these workers, but no additional person-times were added because no deaths were collected prior to 1957. In other words, the annual accumulative doses in each year of follow-up included doses prior to 1957 and all cumulative doses from 1957 to the year of the cumulative dose calculation without adding additional person-times prior to 1957. All exposure records were considered complete (i.e., no missing dose) as any missing dose (lost dosimeter, exposed without a dosimeter, bad read, etc.) was investigated at the time of the occurrence, and an estimate of dose determined, if required, and entered into the individual's exposure record.

As three distinct dosimetry systems were used over the course of the study period, a comprehensive comparison study was performed as each radiation measurement system was replaced. These studies were conducted to evaluate the consistency of dose determination from one system to the next. These study reports are available, to include the manuals and procedures specific to each dosimetry system. Since all eight shipyards included in this study are under the cognizance of the Naval Nuclear Propulsion Program (NNPP), they historically collected and recorded occupational dose in a similar manner (*34–36*).

The primary source of occupational radiation dose to shipyard workers is external exposure to gamma radiation emitted by activated corrosion products, primarily cobalt-60. Most of the exposure comes from inspection, maintenance, and repairs inside the reactor compartments of nuclear-powered ships (*4, 16*). External exposure to neutron radiation was negligible, since overhauls generally occurred after reactors were shut down and reactor shielding designs ensured exposure from neutrons during reactor operation were much less than that from gammas(*37*). Internal exposure was also negligible as only 0.2% of all shipyard workers have ever had a recorded internal exposure. Finally, for all radiation workers that had prior non-NNPP dose (commercial reactor plant, radiographer, etc.) or transferred to another shipyard, all pre-existing exposure was collected from their prior employer, and all historical doses were transferred to the new shipyard location (*38*).

Job History

The occupational code and description of the last job held by everyone in the study were collected through their site's personnel records. Of 437,937 workers in the cohort, 96.7% had their last job specified, while only 3.30% (14,443) did not. In this study, the detailed job groups were not used in analysis, since the annual radiation doses based on personal monitoring records were available. However, those who worked as painters, welders, machine operators, woodworkers, or electricians and those who worked in transportation jobs were grouped into a ''solvent related job'' category as one of the covariates to control for, since solvents might be a potential confounding factor to radiation risk associated with LHC (*39*). Since there was no solvent measurement or rank available, the definition of ''solvent related job'' might not be precise enough to examine the risk of mortality due to LHC related to solvent exposure. Rather, it was used as a rough control for one of the covariates that might bias the

TABLE 3
General Demographics of the Shipyard Cohort by Radiation Group

Characteristics	Non-radiation workers		Radiation workers	
	Number	Percentage	Number	Percentage
Sex				
Male	227,292	80.0%	149,527	97.1%
Female	56,715	20.0%	4,403	2.9%
Race				
White	162,396	57.2%	93,018	60.4%
Black	44,813	15.8%	13,689	8.9%
Other known	13,129	4.6%	7,734	5.0%
Unknown	63,669	22.4%	39,489	25.7%
Age at death or end of follow-up				
Age <40 years	15,293	5.4%	5,933	3.9%
Age 40-49 years	36,769	12.9%	12,325	8.0%
Age 50-59 years	77,732	27.4%	32,172	20.9%
Age 60-69 years	70,514	24.8%	42,825	27.8%
Age 70-79 years	46,807	16.5%	33,653	21.9%
Age 80+ years	36,584	12.9%	22,519	14.6%
Unknown	308	0.1%	4,503	2.9%
Birth cohort				
<1900	6,960	2.5%	903	0.6%
1900	15,304	5.4%	5,470	3.6%
1910	23,134	8.1%	15,282	9.9%
1920	26,425	9.3%	20,660	13.4%
1930	28,792	10.1%	22,757	14.8%
1940	51,283	18.1%	36,157	23.5%
1950	67,442	23.7%	27,539	17.9%
> = 1960	64,359	22.7%	20,659	13.4%
Unknown	308	0.1%	4,503	2.9%
Social economic status				
Blue collar	172,673	60.8%	83,874	54.5%
Technical	32,649	11.5%	15,894	10.3%
Professional	20,228	7.1%	20,879	13.6%
Administrative	35,903	12.6%	9,728	6.3%
Other	22,554	7.9%	23,555	15.3%
Solvent related jobs†				
Yes	85,829	30.2%	39,981	26.0%
No	198,178	69.8%	113,949	74.0%
Grand total	284,007	100.0%	153,930	100.0%

† Included those who worked as painters, welders, machine workers, woodworkers, electricians, or transportation.

risk analysis of LHC with radiation exposure if not included in the model.

Other Covariates

Personal demographic characteristics adjusted in analyses included gender, race, time dependent attained age, and age at first hire. Race was categorized as white, black, other known race, or unknown race. Workers with missing race were categorized as a separate group of ''unknown race'' in the analyses. This race group was composed of workers with mixed races. Because of the significant proportion of workers with unknown race (25.7% for radiation workers and 22.4% for non-radiation workers) (Table 3), race could only serve as a controlling covariate for analyzing the LHC mortality risk with radiation. However, the association of the LHC risk with race itself, if any, observed in this study would not be valid due to the unknown distribution of races. Socioeconomic status was coded based on an individual's pay grade, education, skill set, and responsibilities related to the worker's last job as described in the original study (*4*). The categories of socioeconomic status included blue collar, professional, technical, and administrative. Those whose socioeconomic status could not be classified into these categories were put into an ''other'' category. These variables were treated either by stratification or by inclusion in models directly in analyses. For radiation workers, the age at hire was the age at the beginning of first radiation job.

Data Analysis

Construction of Time-Dependent Radiation Dose Matrix. Shipyard-related radiation dose measurements began in 1945 with the advent of radiography for inspecting castings and welds. The first overhaul of a nuclear-powered vessel occurred in 1957. A cumulative dose matrix calculated from the annual dose records summarized cumulative dose for each year for a radiation worker during his/her radiation work years between 1945 and 2011. Thus, this cumulative dose matrix was time-dependent and only the accumulative dose in the last year of their radiation work would be equal to the lifetime dose. This time-dependent dose matrix enabled time-dependent dose and lagged exposure-based analyses weighted by person-years. In a time-dependent analyses, the cumulative radiation doses of workers with an LHC death at a given time point were compared to the cumulative radiation dose of reference workers at the same time point, rather than comparing to the lifetime dose of reference workers. This approach was designed to prevent survival bias, where healthy survivors tend to have higher lifetime doses because they lived and worked longer (40). The software SAS© 9.4 was used for establishing this dose matrix (*41*).

Time-dependent Data Preparation with Lagged Exposure

A lagged radiation exposure period of 2 years is presented in the article. Lagging 2 years of radiation exposure was undertaken to remove the influence of exposure in a recent 2-year period prior to an event of interest, e.g., mortality due to LHC. This assumed that the most recent 2 years of radiation exposure, if any, were not relevant to the event due to a latency effect. Since the radiation doses in this paper were time-dependent, so also should the exposure lagging. Time-dependent exposure lagging was performed at time of comparison during follow-up using everyone's time-dependent cumulative dose matrix, most often before lifetime dose was reached. Thus, exposure lagging was not necessary to remove recent exposure from lifetime dose; a dose, accumulated to a certain year during the follow-up, was available depending on the event year. This complicated construction of a lagged radiation dose matrix was accomplished using the DATAB module of the EPICURE© software (*42*). This DATAB module created a structure of cross tables by categories of with lagged cumulative dose of 2 years. Variables used for DATAB matrix included sex (male and female), race (white, black, other known race, or unknown race), solvent related job (yes vs. no), birth year (5-year intervals), attained age (5-year intervals), and calendar year (5 year intervals). The birth year (5-year intervals), attained age (5-year intervals), and calendar year (5-year intervals) were time scales used in the tabulations. The dose categories were created in a time-dependent manner, by 25 mSv intervals up to 300 mSv. Doses at 300 mSv and above were categorized in one group due to the very small number of workers under study exposed to a lifetime dose higher than 300 mSv in U.S. shipyards. Workers (2.9% of total) with missing birth dates were automatically excluded from analyses because attained ages could not be calculated for them.

Comparison of Radiation and Non-Radiation Workers

Radiation workers were compared to non-radiation workers using the mortality risks of LHC and its types, controlled for sex, race, calendar time (as a time scale variable in time-dependent analysis), and time-dependent age (an age changing with calendar time). These analyses did not involve radiation dose but were a simple comparison of the disease risks of workers who ever had a radiation job vs.

workers who never had a radiation job. Since there were some workers who had radiation jobs but had never had measurable radiation exposure (zero dose), radiation workers, excluding those with zero radiation dose, were also compared with non-radiation workers separately. AMFIT module of the EPICURE© software (*42*) was used for this analysis.

Dose-response Analysis Based on Time-dependent Categorical Doses and Linear Trend Test

The analyses were performed using the population of 153,930 radiation workers. Due to the concern of comparability of radiation and non-radiation workers, the analysis using radiation workers only was considered more reliable when examining a dose-response relationship. Radiation workers who had 0 mSv time-dependent radiation dose were used as the reference population. A 0 mSv time-dependent radiation dose means that either the worker was hired for a radiation job but had never been exposed to occupational radiation, or at the time of time-dependent analysis, the worker had not been exposed to any radiation yet, although he or she may have a radiation dose later. The final time-dependent radiation dose categories used in Poisson regression models were 0, >0–<25, 25–<50, 50–<100, 100–<200, and > = 200 mSv with 0 mSv as reference. Workers with lifetime radiation dose > = 200 mSv had a median lifetime dose at 249 mSv, which means half of the workers had lifetime radiation dose between 200 and 249 and the other half >249 mSv. The 2 year lagged RRs by dose categories were presented for LHC and its types except for other lymphoid leukemia (7 deaths) and other myeloid leukemia (13 deaths). The number of deaths for these two types were too small to generate stable results in the dose response analysis.

All analyses in this section were stratified by sex, calendar time (5-year interval), and time-dependent attained age group (5-year interval) and controlled for race group, socioeconomic status, solvent related jobs, and age at first hire (for a radiation job) in the model directly. DATAB module of the EPICURE© software (*42*) was used to create the analytical person-year tables stratified by these variables using the categories described above. AMFIT module of the EPICURE© software (*42*) was used for categorical dose analyses with the analytical person-year tables created. This categorical risk analysis shows the actual shape of dose-response curves in figures using the midpoint of each radiation dose category at 0, 12.5, 37.5, 75 and 150 mSv, respectively, except for the highest dose category (> = 200 mSv) where the median dose 249 mSv was used. The sample size weighted linear trend tests for RRs over the midpoint/median doses for each dose category were performed using the Chi-squared method with Epi-Info 7.2.4.0 Software (*43*). The P values of the linear trend tests were presented with the categorical dose analysis results.

Dose-response Analysis based on Time-dependent Continuous Doses

The analyses in this section were performed only for radiation workers for the same reason described above. Instead of using categorical doses, individual time-dependent radiation doses were used as a continuous variable. The dose-response analysis based on continuous doses enable a researcher to assume a desired underlying shape of response curve. Several studies have used Poisson linear ERR models for radiation and cancer research and the underlying dose-response curves for LHC, especially leukemia, were assumed to be linear (*1, 18, 22–24*). However, some other studies suggest the dose-response curves for leukemia are linear quadratic (*13, 24*). We performed a series of tests on choosing appropriate dose-response models: linear, quadratic, or linear quadratic, using leukemia less CLL. Based on the goodness of fit indicator, deviance, and comparison with the categorical dose analysis, the testing result did not support a quadratic or linear quadratic dose-response pattern in the present data. The linear model was best among the three. The results generated were presented in ERR per Sv (ERR/Sv) for comparison purposes, as well as in ERR and RR at 100 mSv to avoid misleading information, since 96.4% of person-years followed among radiation workers were below 100 mSv. All analyses were stratified by sex, calendar time (5-year interval), and time-dependent attained age group (5-year interval) and controlled for race group, socioeconomic status, solvent related jobs, and age at first hire for a radiation job in the model directly. AMFIT module of the EPICURE© software (*42*) was used for this analysis.

RESULTS

General Results of the Cohort Follow-up

Table 2 provides a general description of the study cohort by radiation and non-radiation work status. There are a total of 437,937 participants, comprised of 284,007 (64.9%) non-radiation workers and 153,930 (35.1%) radiation workers. There are 138,912 recorded deaths over the 13,393,399 person-years of follow-up. The average follow-up periods are 29.9 and 31.8 years for non-radiation and radiation workers, respectively. The average employment durations for non-radiation and radiation workers are 10.8 years and 19.4 years, respectively. As described previously, the follow-up for radiation workers began on the date of first radiation work or January 1, 1957, whichever was later. The employment periods prior to radiation jobs contributed to the longer duration of radiation worker employment as seen in Table 2. The median, 75th percentile, and 95th percentile lifetime radiation doses are 0.82 mSv (0.082 rem), 10.71 mSv (1.071 rem), and 83.63 mSv (8.363 rem), respectively. Although the average lifetime occupational radiation dose was 15.36 mSv, most radiation workers have extremely low doses with a small proportion (~25%) of radiation workers with total lifetime doses greater than 10 mSv (1 rem).

Table 3 provides selected demographics of the study cohort, including gender, race, and age at death or at the end of follow-up period if still alive (i.e., 2011), birth cohort, socioeconomic status, and solvent-related jobs. Males constituted 97.1% of radiation workers and 80.0% of non-radiation workers. Both radiation and non-radiation workers are predominantly white. The distribution of age at death or at the end of follow-up (if alive) shows that 45.7% of non-radiation workers and 32.8% of radiation workers are under age 60. Also, 46.4% of non-radiation workers were born in or after 1950, while only 31.3% of radiation workers were born in or after 1950. More than half of workers are classified as blue collar; the proportion of blue-collar workers for radiation workers is slightly lower than non-radiation workers. Proportions of solvent-related jobs are similar between the two groups. All variables presented in Table 3 are considered potential confounders and are adjusted in the multivariate analyses.

Table 4 shows the breakdown of cause-specific LHC deaths relative to time-dependent person-years of follow-up and time-dependent dose groups lagged for 2 years. There is a total of 3,699 LHC deaths (2,225 from non-radiation and 1,474 from radiation workers) recorded during the 54 years of follow-up (1957-2011), which represents 0.84% of the total cohort population. 96.4% of radiation workers have a

time-dependent radiation dose, lagged 2 years, below 100 mSv. Among the LHC types, 39.2% (1,450) of the LHC deaths in the total cohort are due to Hodgkin's or non-Hodgkin's lymphoma, 37.4% (1,382) to leukemia, 17.3% (641) to multiple myeloma, 5.9% (219) to myeloproliferative and myelodysplastic disease, and 0.2% (7, not shown in the table) could not be classified into types. When evaluating only radiation workers, 38.3% (564) of the LHC deaths are due to Hodgkin's or non-Hodgkin's lymphoma, 37.0% (545) to leukemia, 17.8% (263) to multiple myeloma, and 6.7% (99) to myeloproliferative and myelodysplastic disease. Table 4 also shows that with increasing time-dependent radiation doses, deaths for LHC and its types and time-dependent person-years decrease. Therefore, in order to ensure that there would be enough study power to obtain more precise estimates of the categorical RRs, the time-dependent radiation doses are collapsed into the following five dose categories (>0–<25, ≥25–<50, ≥50–<100, ≥100–<200, and ≥200 mSv) for subsequent categorical dose-response analysis compared to 0 mSv category.

Comparison of Radiation and Non-Radiation Workers

Table 5 presents RRs of LHC and its types in two comparisons: 1. radiation vs. non-radiation workers, and 2. radiation workers with greater than 0 mSv lifetime dose vs. non-radiation workers, stratified by sex, calendar time (5-year interval), and time-dependent age group (5-year interval) and controlled for race group in the Poisson regression models. The second comparison excludes radiation workers without measured occupational radiation dose, thereby representing a ''true'' radiation worker group to compare with non-radiation workers. The results in Table 5 show that when the radiation worker group and the non-radiation worker group are compared, LHC (RR = 0.927, P = 0.030), lymphoid leukemia (RR = 0.748, P = 0.011) and lymphomas (R = 0.886, P = 0.031) have RRs that are significantly lower than that of the non-radiation workers' group. Radiation workers show protective RRs' or less chance of mortality due to LHC (6.3% less), lymphoid leukemia (25.2% less), and lymphomas (11.4% less) than non-radiation workers after adjustment for potential confounders. The other types do not present any difference with statistical significance. To evaluate whether the large number of radiation workers with 0 mSv lifetime dose within the radiation worker group might have diluted the mortality risk due to radiation, the RRs between radiation workers with greater than 0 mSv lifetime dose is compared to the non-radiation workers' group. The radiation workers with greater than 0 mSv lifetime dose also show lower risk for LHC (RR = 0.919, P = 0.028) with statistical significance compared to non-radiation workers. Among types, leukemia (RR = 0.880, P = 0.044), especially lymphoid leukemia (RR = 0.658, P = 0.002) show RRs lower than 1 with significance. For the rest of LHC types, the differences between the two comparison groups are not statistically significant (Table 5).

Dose-response Analysis Based on Time-dependent Categorical Doses and Linear Trend Test

Tables 6a–c display the results for the following two categorical analyses: 1. a one-to-one comparison of each dose category group versus the 0 mSv group for LHC and its types to identify any risk in the subset and 2. the P values for categorical dose linear trend (i.e., RR) test for LHC and each of its types weighted by sample sizes in groups in comparison.

The RRs for the following five LHC dose categories relative to the 0 mSv control group when lagged for 2 years were 0.960, 0.914, 1.104, 1.067 and 1.143, respectively, with a linear trend P value of 0.380 (Table 6). A graphical representation of the LHC categorical results are shown in Fig. 1. The RRs for leukemia less CLL for the same evaluation criteria were 0.930, 1.040, 1.132, 1.208 and 1.356, respectively, without statistically significant linear trend (P = 0.253). A graphical representation of the leukemia less CLL categorical results are shown in Fig. 2. The remainder of LHC types did not present any significant linear trending, either.

None of the RRs for any of the dose categories vs. 0 mSv, for any of the cancer types or diseases, show any statistical significance, except for chronic myeloid leukemia which shows a significant elevation of RR at 50–<100 mSv category (RR: 2.746; 95% CI: 1.002, 7.521; P = 0.049) and Non-Hodgkin's lymphoma which shows RRs with borderline significance in categories of 50–<100 mSv (RR: 1.391; 95% CI: 0.954, 2.027; P = 0.087) and 100–<200 mSv (RR: 1.499, 95% CI: 0.975, 2.305; P = 0.065) vs. 0 mSv, respectively. This has resulted in the RR in 100–<200 mSv category for lymphoma (most of them are Non-Hodgkin's type) to be borderline significant (RR = 1.459; 95% CI: 0.965, 2.205; P = 0.073) and an elevated RR for the category 50–<100 mSv (RR = 1.323; 95% CI: 0.919, 1.905; P = 0.132).

One important finding in this section is that for LHC, leukemia less CLL, acute myeloid leukemia, lymphomas, and non-Hodgkin's lymphoma, there are often RRs lower than 1.000 observed in the categories >0–<25 or/and 25–<50 mSv vs. 0 mSv. Although the difference of RRs in these categories are not statistically significant from the reference group (0 mSv), they are consistently lower than 1.000 across LHC and its types (Table 6).

Dose-response Analysis based on Time-dependent Continuous Doses

The results of the dose-response analysis based on time dependent continuous radiation doses lagged 2 years are presented in Table 7. The results presented in ERR/Sv are for purposes of comparisons with other studies, since ERR/

TABLE 4
Causes of Death by Time-dependent Dose Category Lagged 2 Years, 1957–2011

Time-dependent radiation dose lagged 2 years	LHC	Leukemia	Leukemia less CLL	Lymphoid leukemia (LL)	Acute lymphoid leukemia (ALL)	Chronic lymphoid leukemia (CLL)	Other lymphoid leukemia (OLL)	Myeloid leukemia (ML)	Acute myeloid leukemia (AML)	Chronic myeloid leukemia (CML)
Non-radiation	2,225	837	667	242	46	170	26	379	273	84
Radiation dose 0 mSv	385	152	116	43	6	36	1	66	54	11
>0–<25 mSv	823	290	242	64	11	48	5	150	108	32
25–<50 mSv	90	41	31	11	1	10	0	22	16	6
50–<75 mSv	56	20	18	3	0	2	1	12	7	4
75-<100 mSv	35	10	10	0	0	0	0	9	6	2
100-<125 mSv	20	6	6	0	0	0	0	5	5	0
125-<150 mSv	13	5	5	0	0	0	0	3	3	0
150-<175 mSv	15	7	7	1	1	0	0	4	4	0
175-<200 mSv	11	2	2	0	0	0	0	1	0	1
200-<225 mSv	11	4	3	1	0	1	0	2	2	0
225-<250 mSv	4	3	3	0	0	0	0	2	2	0
250-<275 mSv	3	2	1	1	0	1	0	1	0	1
275-<300 mSv	3	2	2	0	0	0	0	1	1	0
> = 300 mSv	5	1	0	1	0	1	0	0	0	0
Total	3,699	1,382	1,113	367	65	269	33	657	481	141

Sv (or ERR/Gy) is the most widely used risk unit in published literature related to radiation and cancer and demonstration of time dependent continuous radiation dose-response relationship with LHC and its types. ERRs/Sv are 0.941 for LHC (95% CI: –0.368, 2.250; P = 0.159) and 1.775 (95% CI: –0.851, 4.401; P = 0.185) for leukemia less CLL, similar to what has been observed in categorical dose-response linear trend tests.

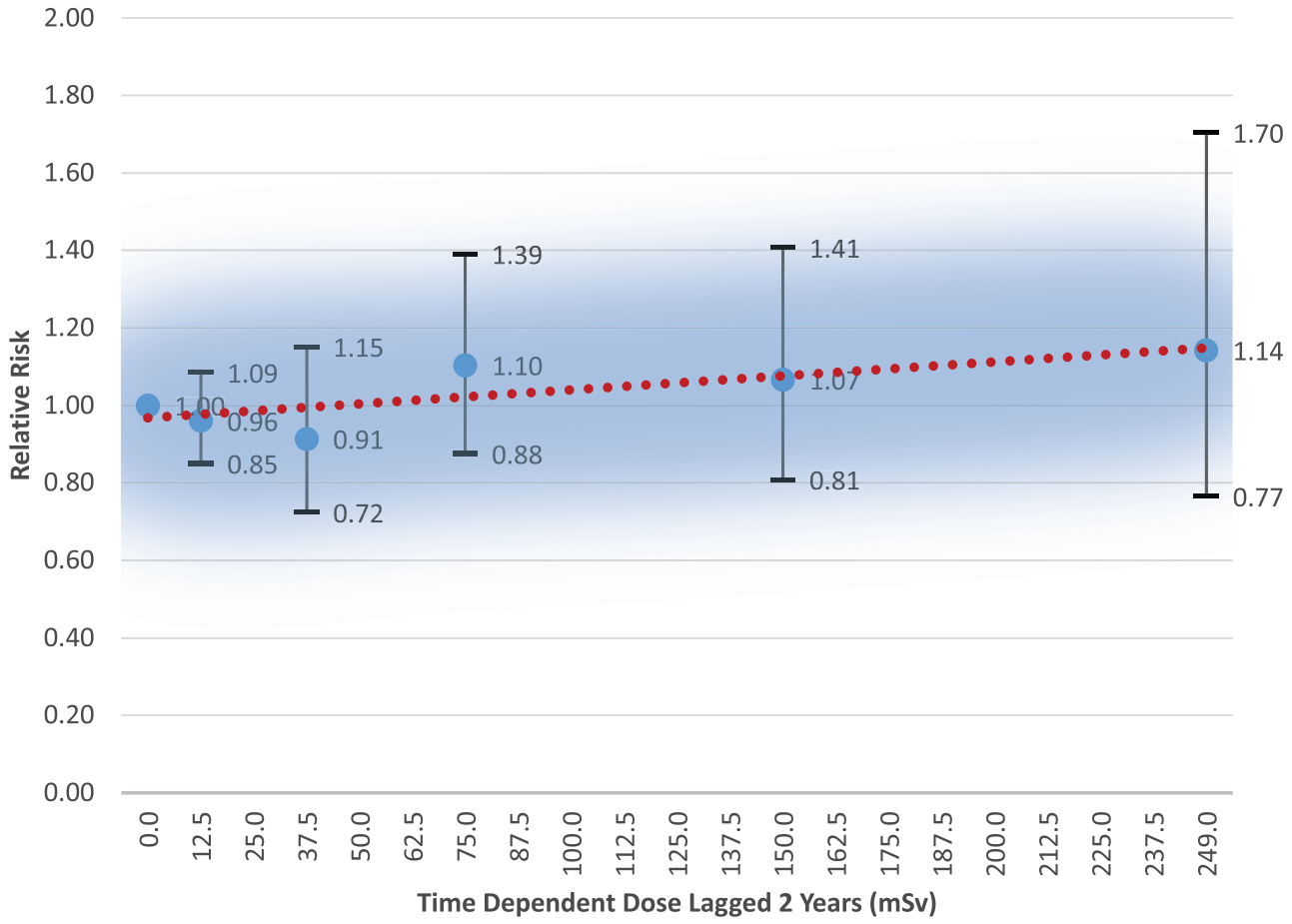

FIG. 1. Relative risks (RR) and 95% confidence intervals (CI) of LHC with time-dependent dose lagged 2 years.

TABLE 4
Extended.

Other myeloid leukemia (OML)	Other leukemia less LL and ML	Multiple myeloma (MM)	Hodgkin's and non-Hodgkin's lymphomas	Hodgkin's lymphoma (HL)	Non-Hodgkin's lymphoma (NHL)	Myeloproliferative and Myelodysplastic	Sum of person-year person-years	% among radiation workers	Cumulative % among radiation workers
22	216	378	886	100	786	120	8,357,107		
1	43	68	135	15	120	29	1,268,776	26.3%	26.3%
10	76	148	325	28	297	58	2,845,519	59.1%	85.4%
0	8	17	27	4	23	5	305,381	6.3%	91.7%
1	5	12	22	1	21	2	142,192	3.0%	94.7%
1	1	5	16	1	15	4	83,573	1.7%	96.4%
0	1	4	9	0	9	1	51,131	1.1%	97.5%
0	2	1	7	1	6	0	35,920	0.7%	98.2%
0	2	2	6	1	5	0	25,126	0.5%	98.8%
0	1	3	6	0	6	0	17,830	0.4%	99.1%
0	1	1	6	2	4	0	12,787	0.3%	99.4%
0	1	0	1	0	1	0	9,404	0.2%	99.6%
0	0	1	0	0	0	0	7,029	0.1%	99.7%
0	1	0	1	0	1	0	5,154	0.1%	99.8%
0	0	1	3	0	3	0	7,389	0.2%	100.0%
35	358	641	1,450	153	1,297	219	13,174,318	100.0%	

As mentioned earlier, 96.4% of person-years followed among radiation workers under study were below 100 mSv. Table 7 presents the ERRs and RRs for LHC and its types at 100 mSv. RR for LHC at 100 mSv is 1.094 (95% CI: 0.963, 1.225; P = 0.159). Leukemia less CLL has an RR at 1.178 (95% CI: 0.915, 1.440; P = 0.185) at 100 mSv. Other types with RRs above 1.000 included myeloid leukemia at 1.283 [95% CI: 0.921, 1.644 (acute at 1.308, 95% CI: 0.883, 1.732, and chronic at 1.356, 95% CI: 0.484. 2.227)], multiple myeloma at 1.004 (95% CI: 0.731, 1.277), and lymphomas at 1.233 [95% CI: 0.988, 1.478 (Hodgkin's at 1.317 and non-Hodgkin's at 1.227) at 100 mSv.

DISCUSSION

This study followed 437,937 workers, including 153,930 radiation workers in eight U.S. nuclear capable shipyards from January 1, 1957, to December 31, 2011. Among the many interesting findings in this study, the following are highlighted.

Lower LHC Risk in Radiation Workers vs. Non-Radiation Workers

The first key finding is that shipyard radiation workers had a significantly lower risk of LHC mortality relative to

TABLE 5
Adjusted Relative Risks for Radiation and Non-Radiation Workers, 1957–2011†

Cancer site	Total deaths	%	Radiation workers vs. non-radiation workers				Radiation workers with >0 dose vs. non-radiation workers			
			RR	RR 95% CI		P value	RR	RR 95% CI		P value
All lymphohematopoietic cancers (LHC)	3,699	100.0	0.927	0.865	0.992	0.030	0.919	0.852	0.991	0.028
Leukemia	1,382	37.4	0.911	0.814	1.019	0.105	0.880	0.778	0.997	0.044
Leukemia less CLL	1,113	30.1	0.937	0.827	1.062	0.306	0.927	0.809	1.063	0.280
Lymphoid leukemia (LL)	367	9.9	0.748	0.598	0.936	0.011	0.658	0.508	0.852	0.002
Acute lymphoid leukemia (ALL)	65	1.8	0.646	0.371	1.126	0.124	0.578	0.306	1.091	0.091
Chronic lymphoid leukemia (CLL)	269	7.3	0.810	0.627	1.048	0.108	0.693	0.515	0.934	0.016
Other lymphoid leukemia (OLL)	33	0.9	0.453	0.192	1.070	0.071	0.538	0.215	1.345	0.185
Myeloid leukemia (ML)	657	17.8	1.007	0.857	1.183	>0.500	1.026	0.862	1.221	>0.500
Acute myeloid leukemia (AML)	481	13.0	1.011	0.838	1.220	>0.500	1.001	0.816	1.228	>0.500
Chronic myeloid leukemia (CML)	141	3.8	1.032	0.725	1.470	>0.500	1.110	0.762	1.618	>0.500
Other myeloid leukemia (OML)	35	0.9	0.863	0.416	1.787	>0.500	1.066	0.503	2.261	>0.500
Other leukemia less LL and ML	358	9.7	0.921	0.739	1.147	0.461	0.860	0.673	1.100	0.230
Multiple myeloma (MM)	641	17.3	1.013	0.859	1.194	>0.500	1.010	0.844	1.209	>0.500
Lymphomas	1,450	39.2	0.886	0.793	0.989	0.031	0.907	0.805	1.022	0.109
Hodgkin's lymphoma (HL)	153	4.1	0.784	0.553	1.112	0.172	0.748	0.507	1.105	0.145
Non-Hodgkin's lymphoma (NHL)	1,297	35.1	0.898	0.800	1.009	0.070	0.926	0.817	1.050	0.231
Myeloproliferative and myelodysplastic	219	5.9	1.060	0.803	1.399	>0.500	0.997	0.734	1.355	>0.500

† Stratified by sex, calendar time (5-year interval), and time dependent age group (5-year interval) and controlled for race group in the model.

TABLE 6a
Relative Risks (RR)† of Categorical Cumulative Time-dependent Radiation Dose, Lagged 2 Years among Radiation Workers – 1/3

Cancer site	Dose	RR	95% CI		P value
LHC (1474 deaths)	0 mSv	1.000			
	>0–<25 mSv vs. 0	0.960	0.850	1.085	>0.500
	25–<50 mSv vs. 0	0.914	0.725	1.152	0.444
	50–<100 mSv vs. 0	1.104	0.876	1.390	0.402
	100–<200 mSv vs. 0	1.067	0.808	1.408	>0.500
	> = 200 mSv vs. 0	1.143	0.766	1.704	>0.500
	Sample size weighted categorical linear trend‡				0.380
Leukemia (545 deaths)	0 mSv	1.000			
	>0–<25 mSv vs. 0	0.853	0.699	1.041	0.118
	25–<50 mSv vs. 0	1.043	0.736	1.478	> 0.5
	50–<100 mSv vs. 0	0.913	0.615	1.356	> 0.5
	100–<200 mSv vs. 0	0.907	0.566	1.453	> 0.5
	> = 200 mSv vs. 0	1.343	0.742	2.430	0.329
	Sample size weighted categorical linear trend‡				0.521
Leukemia less CLL	0 mSv	1.000			
(446 deaths)	>0–<25 mSv vs. 0	0.930	0.743	1.164	>0.500
	25–<50 mSv vs. 0	1.040	0.697	1.554	>0.500
	50–<100 mSv vs. 0	1.132	0.745	1.719	>0.500
	100–<200 mSv vs. 0	1.208	0.746	1.955	0.441
	> = 200 mSv vs. 0	1.356	0.684	2.688	0.383
	Sample size weighted categorical linear trend‡				0.253
Lymphoid leukemia	0 mSv	1.000			
(125 deaths)	>0–<25 mSv vs. 0	0.677	0.458	1.001	0.051
	25–<50 mSv vs. 0	1.010	0.517	1.973	>0.500
	50–<100 mSv vs. 0	0.326	0.100	1.055	0.062
	100–<200 mSv vs. 0	0.163	0.022	1.192	0.074
	> = 200 mSv vs. 0	1.173	0.360	3.820	>0.500
	Sample size weighted categorical linear trend‡				0.287
Acute lymphoid leukemia	0 mSv	1.000			
(19 deaths)	>0–<25 mSv vs. 0	0.772	0.280	2.132	>0.500
	25–<50 mSv vs. 0	0.723	0.085	6.119	>0.500
	50–<100 mSv vs. 0				
	100–<200 mSv vs. 0	1.609	0.186	13.952	>0.500
	> = 200 mSv vs. 0				
	Sample size weighted categorical linear trend‡				>0.500

† Stratified by sex, calendar time (5 years), and attained age (5 years) and controlled for race group, SES group, solvent job, and age at first hire.

‡ Test for linear trend using dose level at 0, 12.5, 37.5, 75, 150, and 249 mSv.

non-radiation workers when adjusted for sex, calendar time, time-dependent age, and race (P = 0.030). Among the LHC types, the radiation workers showed an 11.4% less chance of mortality from all lymphomas combined, compared to non-radiation workers (P = 0.031). The analysis also showed a 25.2% less chance of mortality from lymphoid leukemia (P = 0.010).

This finding is consistent with a study that used prior to 1981 data from the same cohort, in which the non-radiation workers had higher risk than radiation workers (*4*). Several plausible explanations for the deficit in LHC mortality in radiation workers compared to non-radiation workers are 1. it is a real deficit effect; 2. the ''healthy worker effect'', or 3. a combination of both. Prior to entry into the radiation worker program, radiation workers must pass an initial medical screening looking for the existence of cancerous conditions. If a cancerous condition is found, the worker is precluded from becoming a radiation worker until the condition is treated and the worker is medically cleared. This medical screening is performed periodically during employment with the frequency of screening increasing with age. This is a form of selection bias, as non-radiation workers do not receive this same service. To rule out the ''healthy worker effect'' in subsequent radiation dose related analyses, only evaluations from within the radiation worker population were carried out, thus, all results in Tables 6 and 7 were not impacted by the ''healthy worker effect''.

LHC Risks in Higher Radiation Dose Subsets of Shipyard Radiation Workers

Although radiation workers had a lower risk of mortality due to LHC than non-radiation workers, further analyses were performed using only the radiation workers to examine if any subset of radiation workers exposed to

TABLE 6b
Relative Risks (RR)† of Categorical Cumulative Time-dependent Radiation Dose, Lagged 2 Years among Radiation Workers – 2/3

Cancer site	Dose	RR	95% CI		P value
Chronic lymphoid leukemia	0 mSv	1.000			
(99 deaths)	>0–<25 mSv vs. 0	0.607	0.393	0.939	0.025
	25–<50 mSv vs. 0	1.051	0.518	2.132	>0.500
	50–<100 mSv vs. 0	0.244	0.058	1.018	0.053
	100–<200 mSv vs. 0				
	> = 200 mSv vs. 0	1.272	0.387	4.175	>0.500
	Sample size weighted categorical linear trend‡				0.366
Myeloid leukemia (278 deaths)	0 mSv	1.000			
	>0–<25 mSv vs. 0	1.019	0.759	1.367	>0.500
	25–<50 mSv vs. 0	1.278	0.784	2.083	0.326
	50–<100 mSv vs. 0	1.456	0.885	2.396	0.140
	100–<200 mSv vs. 0	1.341	0.733	2.451	0.341
	> = 200 mSv vs. 0	1.555	0.669	3.615	0.305
	Sample size weighted categorical linear trend‡				0.145
Acute myeloid leukemia	0 mSv	1.000			
(208 deaths)	>0–<25 mSv vs. 0	0.885	0.635	1.233	0.470
	25–<50 mSv vs. 0	1.115	0.633	1.963	>0.500
	50–<100 mSv vs. 0	1.079	0.584	1.993	>0.500
	100–<200 mSv vs. 0	1.477	0.781	2.793	0.230
	> = 200 mSv vs. 0	1.542	0.611	3.893	0.359
	Sample size weighted categorical linear trend‡				0.128
Chronic myeloid leukemia	0 mSv	1.000			
(57 deaths)	>0–<25 mSv vs. 0	1.389	0.696	2.772	0.352
	25–<50 mSv vs. 0	2.271	0.832	6.202	0.110
	50–<100 mSv vs. 0	2.746	1.002	7.521	0.049
	100–<200 mSv vs. 0	0.716	0.092	5.595	>0.500
	> = 200 mSv vs. 0	1.838	0.234	14.424	>0.500
	Sample size weighted categorical linear trend‡				0.267
Other leukemia less LL and ML	0 mSv	1.000			
(142 deaths)	>0–<25 mSv vs. 0	0.774	0.530	1.130	0.184
	25–<50 mSv vs. 0	0.717	0.335	1.535	0.392
	50–<100 mSv vs. 0	0.653	0.276	1.545	0.333
	100–<200 mSv vs. 0	0.967	0.407	2.298	>0.500
	> = 200 mSv vs. 0	1.184	0.364	3.854	>0.500
	Sample size weighted categorical linear trend‡				>0.500

† Stratified by sex, calendar time (5 years), and attained age (5 years) and controlled for race group, SES group, solvent job, and age at first hire.

‡ Test for linear trend using dose level at 0, 12.5, 37.5, 75, 150 and 249 mSv.

higher doses have an elevated risk of mortality due to LHC. Radiation workers with a 0 mSv radiation dose were used as a reference group when calculating categorical RRs.

LHC as a group did not show any statistically significant elevated RR in any categorical time-dependent doses lagged 2 years at >0–<25, 25–<50, 50–<100, 100–<200, and > = 200 mSv vs. 0 mSv. Among types, chronic myeloid leukemia showed a significant elevation of RR for the 50-<100 mSv category only (RR: 2.746; 95% CI: 1.002, 7.521; P = 0.049) vs. 0 mSv. It might be possible that the risk observed in a single subset may not be valid if the risk did not increase with dose. Any increased or decreased RR in a single dose category could be a result of uncontrolled covariates in that category rather than radiation exposures. Thus, dose-response analysis would be still needed to further evaluate the LHC risks.

Sublinear Categorical Dose-Response Relationship

As seen in Figs. 1 and 2, a curved dose-relationship was not supported. Given the fact that RRs in mid dose categories did not fall into a perfect straight line and had wide confidence intervals, we define this as a quasi or ''sublinear'' dose-response relationship, in which the point that the risk could fluctuate around the straight line and their linearity trends can be tested with linear regression models. However, the radiation doses in the present study were limited to low levels (<250 mSv) and the result of the analysis did not preclude that the dose-response relationship may become quadratic, linear quadratic, or other shapes at higher doses beyond the present study. The problem is that the sample sizes (person-years and deaths) were heavily skewed toward low doses. Even if RRs were observed increasing with dose, the one-to-one categorical dose comparisons and the linear trend tests are not statistically

TABLE 6c
Relative Risks (RR)† of Categorical Cumulative Time-dependent Radiation Dose, Lagged 2 Years among Radiation Workers - 3/3

Cancer site	Dose	RR	95% CI		P value
Multiple myeloma	0 mSv	1.000			
(263 deaths)	>0–<25 mSv vs. 0	1.020	0.764	1.363	>0.500
	25–<50 mSv vs. 0	1.012	0.592	1.729	>0.500
	50–<100 mSv vs. 0	1.191	0.697	2.037	>0.500
	100–<200 mSv vs. 0	1.056	0.541	2.064	>0.500
	> = 200 mSv vs. 0	0.738	0.231	2.355	>0.500
	Sample size weighted categorical linear trend‡				>0.500
Lymphomas (564 deaths)	0 mSv	1.000			
	>0–<25 mSv vs. 0	1.070	0.873	1.310	>0.500
	25–<50 mSv vs. 0	0.779	0.514	1.182	0.241
	50–<100 mSv vs. 0	1.323	0.919	1.905	0.132
	100–<200 mSv vs. 0	1.459	0.965	2.205	0.073
	> = 200 mSv vs. 0	1.417	0.763	2.633	0.270
	Sample size weighted categorical linear trend‡				0.103
Hodgkin's lymphoma	0 mSv	1.000			
(53 deaths)	>0–<25 mSv vs. 0	0.931	0.494	1.754	>0.500
	25–<50 mSv vs. 0	1.173	0.385	3.573	>0.500
	50–<100 mSv vs. 0	0.716	0.162	3.166	>0.500
	100–<200 mSv vs. 0	1.100	0.247	4.894	>0.500
	> = 200 mSv vs. 0	2.945	0.658	13.171	0.158
	Sample size weighted categorical linear trend‡				>0.500
Non-Hodgki's lymphoma	0 mSv	1.000			
(511 deaths)	>0–<25 mSv vs. 0	1.086	0.876	1.346	0.451
	25–<50 mSv vs. 0	0.737	0.470	1.156	0.184
	50–<100 mSv vs. 0	1.391	0.954	2.027	0.087
	100–<200 mSv vs. 0	1.499	0.975	2.305	0.065
	> = 200 mSv vs. 0	1.275	0.644	2.522	0.486
	Sample size weighted categorical linear trend‡				0.129
Myeloproliferative and	0 mSv	1.000			
myelodysplastic	>0–<25 mSv vs. 0	0.876	0.558	1.375	>0.500
(99 deaths)	25–<50 mSv vs. 0	0.655	0.252	1.706	0.386
	50–<100 mSv vs. 0	0.928	0.382	2.257	>0.500
	100–<200 mSv vs. 0	0.222	0.030	1.646	0.141
	> = 200 mSv vs. 0				
	Sample size weighted categorical linear trend‡				0.175

† Stratified by sex, calendar time (5 y), and attained age (5 y) and controlled for race group, SES group, solvent job, and age at first hire

‡ Test for linear trend using dose level at 0, 12.5, 37.5, 75, 150, and 249 mSv

significant, because the number of person-years with mid and high doses were limited. The other problem might be that our dose range among radiation workers was not broad enough to reveal the curvature of a dose-response relationship at higher dose range; thus, the linear pattern identified in our present paper, although not significant, would not preclude a curved dose-response relationship in a higher dose range beyond the doses in this study.

Risk Observation at Low Dose

One interesting observation that we could not ignore in this study was that among LHC and some of its types (leukemia less CLL, acute myeloid leukemia, and lymphomas), there were often RRs lower than 1.00 in the categories >0–<25 or/and 25–<50 mSv vs. 0 mSv. Although the difference of RRs in those categories were not statistically significant compared to the reference (0 mSv), they were consistently observed across LHC and its types. For instance, for LHC as a whole group, the RRs in categories of >0–<25 and 25–<50 mSv vs. 0 mSv are 0.960 and 0.914, respectively. RRs of Leukemia less CLL vs. 0 is 0.930 in dose category of >0–<25 mSv. The RR of acute myeloid leukemia is 0.885 in dose category of >0–<25 mSv. The RR of Non-Hodgkin's lymphoma in category of 25–<50 mSv vs. 0 is as low as 0.737, which is 26.3% lower than the reference group. Although, these results hinted a hormesis like effect below 50 mSv, all individual categorical dose results were not significant and therefore not conclusive. The addition of more radiation worker mortality data in future studies will add more statistical power to the results and further clarify this observation.

Risk Analysis Based on Time-dependent Continuous Doses

Further analysis was done using radiation dose as a continuous variable, so that the dose response analysis could be done at an individual level rather than aggregated

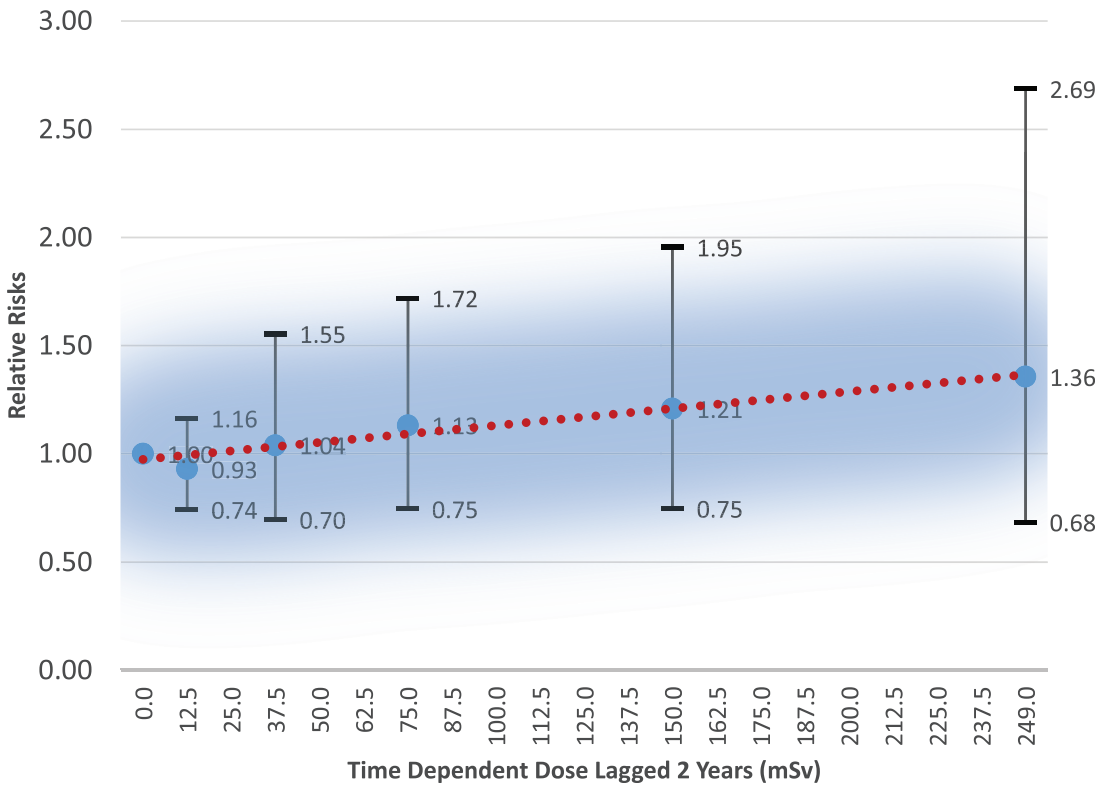

FIG. 2. Relative Risks (RR) and 95% confidence intervals (CI) of leukemia less CLL with time-dependent dose lagged 2 years.

as in categorical analysis. Table 7 presents the result of this analysis using continuous dose by EPICURE in ERR/Sv, ERR at 100mSv, and RR at 100 mSv. The results for linear trends were not statistically significant for LHC or any of its types, although lymphomas came close (P = 0.062). In the shipyard population, an RR in continuous dose analysis would be heavily weighted towards dose-response patterns at low doses, less than 50 mSv, since 91.7% of radiation workers had a dose below this level (Table 4). The small sample sizes in higher dose groups lead to low statistical power of the analysis might be the main problem of the insignificance of the dose response.

The small sample size in the higher dose groups lead to low statistical power and greater uncertainty. The lack of

TABLE 7
Excess Relative Risks (ERR) and Relative Risks (RR) at at 1 Sv or 100 mSv Cumulative Time-dependent Radiation Dose, Lagged 2 Years, Radiation Workers†

Cancer site	P value	ERR at 1 Sv			ERR at 100 mSv			RR at 100 mSv continuous model		
		At 1 Sv	95% CI		At 100 mSv	95% CI		At 100 mSv	95% CI	
All lymphohematopoietic cancers (LHC)	0.159	0.941	–0.368	2.250	0.094	–0.037	0.225	1.094	0.963	1.225
Leukemia	0.385	0.960	–1.207	3.128	0.096	–0.121	0.313	1.096	0.879	1.313
Leukemia less CLL	0.185	1.775	–0.851	4.401	0.178	–0.085	0.440	1.178	0.915	1.440
Lymphoid leukemia (LL)	>0.500	–0.453	–3.364	2.458	–0.045	–0.336	0.246	0.955	0.664	1.246
Acute lymphoid leukemia (ALL)	>0.500	–0.458	–3.435	2.519	–0.046	–0.344	0.252	0.954	0.656	1.252
Chronic lymphoid leukemia (CLL)	>0.500	–0.456	–3.125	2.214	–0.046	–0.313	0.221	0.954	0.687	1.221
Myeloid leukemia (ML)	0.125	2.827	–0.785	6.439	0.283	–0.079	0.644	1.283	0.921	1.644
Acute myeloid leukemia (AML)	0.156	3.077	–1.170	7.324	0.308	–0.117	0.732	1.308	0.883	1.732
Chronic myeloid leukemia (CML)	0.424	3.555	–5.163	12.273	0.356	–0.516	1.227	1.356	0.484	2.227
Other leukemia less LL and ML	>0.500	0.445	–3.563	4.453	0.045	–0.356	0.445	1.045	0.644	1.445
Multiple myeloma (MM)	>0.500	0.037	–2.695	2.770	0.004	–0.269	0.277	1.004	0.731	1.277
Lymphomas	0.062	2.331	–0.115	4.777	0.233	–0.012	0.478	1.233	0.988	1.478
Hodgkin's lymphoma (HL)	0.488	3.167	–5.776	12.110	0.317	–0.578	1.211	1.317	0.422	2.211
Non-Hodgkin's lymphoma (NHL)	0.081	2.266	–0.280	4.812	0.227	–0.028	0.481	1.227	0.972	1.481
Myeloproliferative and myelodysplastic	>0.500	–0.445	–3.810	2.920	–0.044	–0.381	0.292	0.956	0.619	1.292

† Stratified by sex, calendar time (5 years), and attained age (5 years) and controlled for race group, SES group, solvent job, and age at first hire.

TABLE 8
Excess Relative Risk of Leukemia less CLL in Comparison with Other Studies

Studies	Population	Risk indicator	Leukemia less CLL	Exposure lagging
Cardis et al. (*2*)	15 Countries	ERR/Sv	1.93 (<0.00, 8.47)†	Lagged 2 years
Muirhead et al. (*6*)	3rd UK NRRW	ERR/Sv	1.712 (0.06, 4.29)†	Lagged 2 years
Leuraud et al. (*23*)	INWORKS (France, UK and U.S.)	ERR/Gy	2.96 (1.17, 5.21)†	Lagged 2 years
Schubauer-Berigan et al. (*18*)	INWORKS (U.S. pooled)	ERR/Sv (ERR %/10 mSv)	1.70 (–0.22, 4.70)‡	Lagged 7 years
Present study	U.S. shipyard workers	ERR/Sv	1.775 (–0.851, 4.401) ‡	Lagged 2 years

† 90% Confidence intervals.
‡ 95% Confidence intervals.

adequate data points may be a main contributor in the lack of any significance for this analysis. The inclusion of additional mortality data in future analysis may provide further clarification; however, the magnitude of risks in the continuous analysis were still comparable to that in the previous categorical analyses. For example, leukemia less CLL had an RR of 1.178 (95% CI: 0.915, 1.440; P = 0.185) at 100 mSv in the continuous analysis, which was between the 1.132 for 50–<100 mSv and 1.208 for 100–<200 mSv lagged 2 years in the categorical analysis. Therefore, this study will be repeated when addition mortality data becomes available.

Comparison with Other Epidemiologic Studies

Table 8 summarizes ERR/Sv and ERR/Gy for leukemia less CLL, the most common LHC type reported in published studies on radiation risk among workers. The ERRs per Sv range from 1.70 (90% CI –0.22, 4.70) to 2.96 (90% CI: 1.17, 5.21) from several large-scale epidemiological studies around the world (*1, 6, 18, 23*). In these studies, various lag periods from 0 to 10 years were used. For comparison purposes, the ERR/Sv after lagging 2 years for leukemia less CLL observed in the present study is used in Table 8. The INWORKS (France, UK and U.S.) (*23*) had the highest ERR/Sv at 2.96 (90% CI: 1.17, 5.21). In 2021, the U.S. pooled INWORKS reported an even higher ERR/Sv at 3.15 (90% CI: 1.15,5.72) for leukemia (including CLL) (*8*). However, the U.S. pooled INWORKS study (*44*) showed lower and statistically nonsignificant ERR/Sv at 1.70 (95% CI: –0.22, 4.70) (*44*). ERR/Sv for leukemia less CLL is 1.775 (95% CI: –0.851, 4.401) in the present study, which is consistent with the other studies in the table and particularly close to 1.712 (95% CI: 0.06, 4.29) in the 3rd UK NRRW study by Muirhead et al. (*6*) and 1.70 (95% CI: –0.22, 4.70) in the U.S. pooled INWORKS study by Schubauer-Berigan et al. (*18*). This comparison suggests that the slope of the dose-response relationship in U.S. shipyard workers is similar to that in other radiation workers in those studies.

While the present study analyzed LHC types in detail, three other published studies looked at some but not all the same LHC types on low-dose radiation exposures (*9, 18, 23*). A comparison of the findings of these studies is presented in Table 9. While the INWORKS study (*23*) showed that the ERR/Sv of chronic myeloid leukemia was much higher than that for acute myeloid leukemia (10.45 versus 1.29), the present study showed comparable results (3.555 vs. 3.077). The ERR/Sv for multiple myeloma was found to be elevated in the U.S. pooled INWORKS study at 3.90 (95% CI: 0.60, 9.60) (*18*), but reduced to a much lower level when combined with UK and France, 0.84 (90% CI: –0.96, 3.33) (*23*). The most recent update on NRRW-3 cohort showed that ERR/Gy for multiple myeloma was 1.50 (95% CI: –0.42, 5.60) without statistical significance (*9*). The INWORKS study observed ERR/Sv of 2.94 for Hodgkin's lymphoma and 0.47 for non-Hodgkin's lymphoma (*23*), while NRRW-3 cohort showed negative association for Hodgkin's lymphoma but positive association for non-Hodgkin's lymphoma at 1.31 (95% CI: –0.25, 3.77) (*9*). None of the values in either study achieved statistical significance. In the present study, ERR/Sv was 3.167 (–1.000, 12.110) for Hodgkin's lymphoma (very close to INWORKS 2.94 ERR/Gy) and 2.266 (–0.280, 4.812) for non-Hodgkin's lymphoma (close to NRRW-3 1.31 ERR/Gy), both without significance. Berrington de Gonzalez et al. compared mortality rates of 43,763 radiologists and 64,990 psychiatrists who were followed from 1979 to 2008 (*45*). This study reported a significantly increased RR for non-Hodgkin's lymphoma of 2.69 (95% CI 1.33–5.45) for radiologists vs. psychiatrists. These findings might indicate some need for further investigation regarding the association of non-Hodgkin's lymphoma with radiation exposure.

It is important to point out that this population has had very low radiation exposure. Although some of the dose categories presented some risks with certain cancers, the actual number of workers exposed in those categories were small. In addition to what has been presented in Table 2, the 95 percentile of lifetime radiation dose was at 83.63 mSv. Figure 3 shows the average annual radiation dose distribution and number of workers exposed by calendar year from 1957 to 2011. This graph shows two periods of peak employment: one large peak from 1964 to 1970 and a smaller peak from 1982 to 1992. The average annual radiation doses were between 0.0025 and 0.0060 Sv before 1980, decreased to below 0.0020 Sv in 1980 and further decreased to below 0.0010 Sv in 1995 and thereafter. Most importantly for this study, this suggests that the radiation exposures among workers hired after 1979 were at relatively lower levels compared to workers hired before 1979.

TABLE 9
Excess Relative Risk (ERR) Comparison among Different Large-Scale Studies on Low-Dose Radiation

Studies	Leuraud et al. (*23*) - lagged 2 years	Schubauer-Berigan et al. (*18*) - lagged 10 years	Hunter et al. (*9*) - lagged 10 years	Present study - lagged 2 years
Population	INWORKS (France, UK and U.S.)	U.S. pooled (INWORKS)	NRRW-3	U.S. shipyard workers
Risk indicator	ERR/Gy	ERR/Sv	ERR/Gy	ERR/Sv
Confidence intervals	90%	95%	95%	95%
Lymphoid leukemia (LL)	5.8 (n/a, 31.57)			–0.453 (–1.000, 2.458)
Acute myeloid leukemia (AML)	1.29 (–0.82, 4.28)			3.077 (–1.000, 7.324)
Chronic myeloid leukemia (CML)	10.45 (4.48, 19.65)			3.555 (–1.000, 12.273)
Other leukemia less LL and ML				0.445 (–1.000, 4.453)
Multiple myeloma (MM)	0.84(–0.96, 3.33)	3.90 (0.60, 9.60)	1.50 (–0.42, 5.60)	–0.037 (–1.000, 2.770)
Hodgkin's and Non-Hodgkin's lymphomas		1.8 (0.027, 4.40)		2.331 (–0.115, 4.777)
Hodgkin's lymphoma (HL)	2.94 (n/a, 11.49)		<-1.93 (<–1.93, 26.6)	3.167 (–1.000, 12.110)
Non-Hodgkin's lymphoma (NHL)	0.47(–0.76, 2.03)		1.31 (–0.25, 3.77)	2.266 (–0.280, 4.812)

Analysis of Covariates

RRs for each covariate are not presented in this study as some covariates were not sufficiently well-defined to generate reliable RRs. For instance, race was categorized as white, black, other known race, or unknown race. Ideally, only three categories should exist (white, black, other) based on shipyard worker demographics and number of workers in each category. However, since a quarter of the population had unknown race, any analysis results for this covariate would have been unreliable. Although specific covariate results are not presented, it did not prevent their use in the statistical analysis for controlling purposes only.

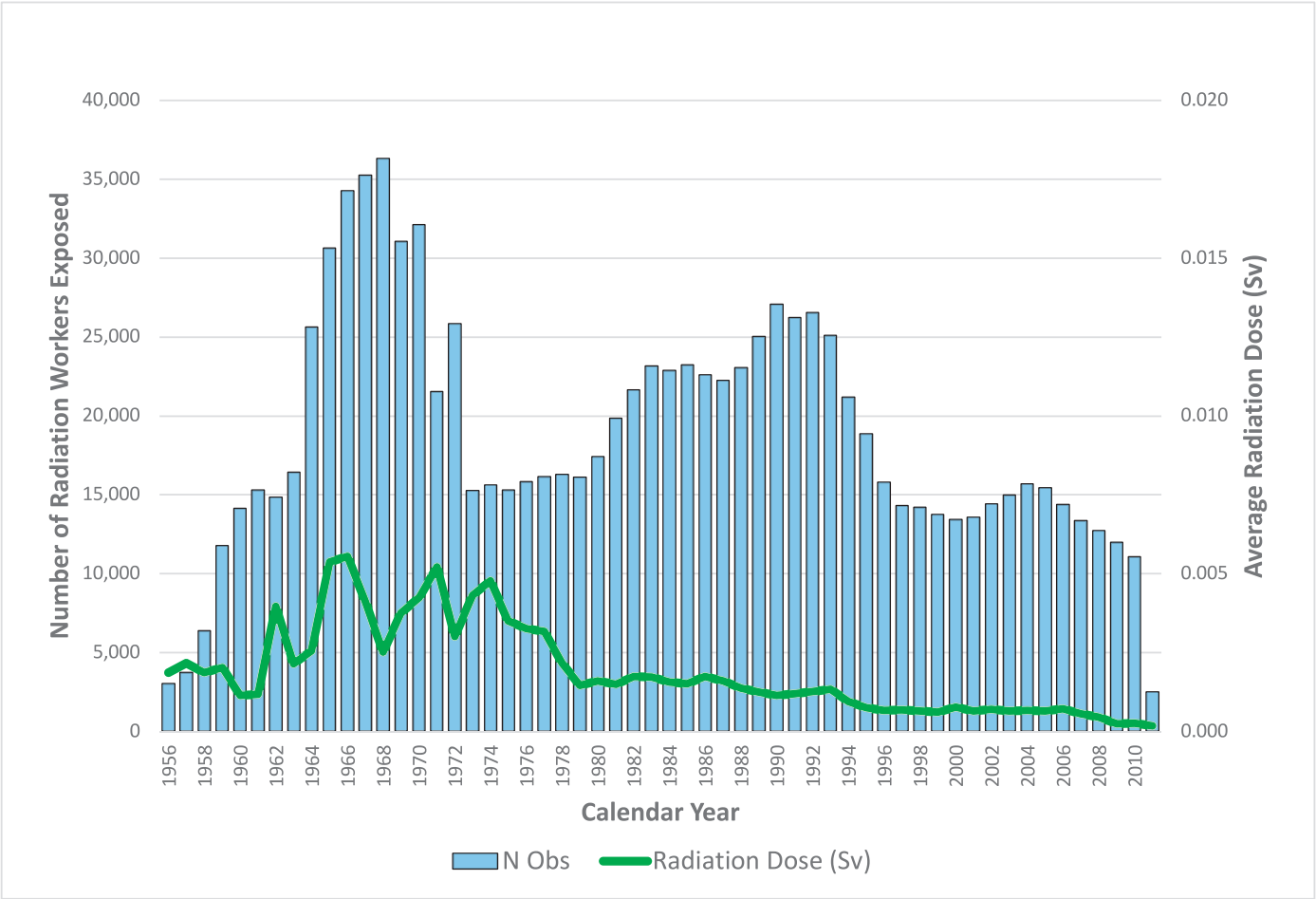

FIG. 3. Distribution of average annual radiation dose and number of workers exposed by calendar year.

Background Radiation Exposure

As described in the methods section, the radiation data in this study refers to occupational radiation exposure after background (i.e., environmental) correction. Thus, the occupational radiation dose is not total annual dose (occupational, background, medical, etc.) to the individual. It was assumed that, for other than occupational exposure, that both radiation and non-radiation workers were exposed to similar background exposure scenarios while working in the shipyard (e.g., environmental, medical, industrial). As some of these exposure scenarios can vary based on age or year of employment, for example, advances and increased use of medical diagnostics and nuclear medicine, controlling for time-dependent age and calendar time was imperative to minimizes these effects in the analysis.

Strengths and Limitations

The strengths of the present study include: 1. a total of 437,937 workers enrolled, representing one of the largest cohorts with the longest follow-up time among studies to date for LHC risk among radiation workers. The resultant increased reliability and statistical power are critical for low mortality cancers such as LHC; 2. detailed annual radiation dose measurements were available for each radiation worker during their entire follow-up period, thereby allowing sophisticated exposure analyses; 3. all occupational radiation exposures examined were from the single industry of shipyard workers, thereby avoiding the issue of variation in type of radiation examined, which complicated other past studies; 4. time-dependent radiation doses were used in our analyses, which dramatically increased the validity and accuracy of the associated measurements, since the radiation dose varied by time; 5. the exposure lagging analyses were used to deal with the latent period issue of cancers, which further improved the reliability of our study; and 6. the present study used both categorical and linear dose-response models using continuous individual doses, an approach widely accepted by cancer epidemiologists (*1, 6, 18, 22–24, 46)* so that the results are comparable to other major studies.

The limitations of the present study include: 1. missing race information on a quarter of the cohort population, which prevented reliable covariate analyses; 2. approximately three percent of radiation workers had to be excluded from the analysis due to missing birth dates reducing the statistical power of the analysis; 3. use of the last job, instead of the longest job or full job history, to assign the solvent-related jobs, which might have led to uncontrolled residual risk; 4. deaths, rather than incident cases, were used, which leads to an underreporting of cases, since treatment for LHCs, has been increasingly successful; 5. cancer causes were based on National Death Index reports/Death Certificates, rather than on pathology reports, which might have limited the ability to examine LHC types. LHC information might be missing due to lacking details; 6. low number of person-years with doses in the upper range of the dose analysis; 7. the potential influence from unknown background radiation; and 8) the completeness of follow-up, since the death search was the only method to follow up workers for LHC cancers.

In summary, this study found that: 1. the risks of LHC and its types were not elevated in radiation workers compared to non-radiation workers as a group in U.S. nuclear shipyards; 2. ERR at 100 mSv for LHC and leukemia less CLL was in line with other low dose radiation studies and 3. although this was a relatively large study, that additional mortality data is needed to draw any further significant conclusions on low dose LHC mortality risks.

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