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Chronic lymphocytic leukaemia and radiation: findings among workers at five US nuclear facilities and a review of the recent literature

Mary K. Schubauer-Berigan, Robert D. Daniels, Donald A. Fleming, Andrea M. Markey, James R. Couch, Steven H. Ahrenholz, Jenneh S. Burphy,*[1] Jeri L. Anderson and Chih-Yu Tseng

National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati, OH, USA

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Correspondence: Mary K. Schubauer-Berigan, NIOSH, DSHEFS, MS-R15, 5555 Ridge Ave, Cincinnati, OH 45213, USA.

E-mail: zcg3@cdc.gov

*Present address: Martin County Health Department, Stuart, FL 34994, USA

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Summary

The aetiology of chronic lymphocytic leukaemia (CLL) is largely unknown. Despite compelling evidence for ionising radiation as a cause of most forms of leukaemia, CLL was not found to be radiogenic in early studies. Herein we describe the recent evidence for causation of CLL by ionising and non-ionising radiation, including a nested case-control study conducted within a cohort of 94 517 US workers at four nuclear weapons facilities and a nuclear naval shipyard. Forty-three cases of CLL deaths and 172 age-matched controls were identified with follow-up up to between 1990 and 1996. Radiation exposure from external sources and plutonium (lagged 10 years) was assessed for each worker, based on monitoring records. The excess relative rate (ERR) was estimated for workers receiving elevated doses compared to unexposed workers, controlling for possible risk factors. The ERR per 10 mSv was −0·020 (95% confidence interval: <0, 0·14) based on all exposed workers. However, for workers receiving <100 mSv, the ERR per 10 mSv was 0·20 (−0·035, 0·96). Recent studies of uranium miners and other populations have shown elevations of CLL possibly associated with ionising and non-ionising radiation. New studies should use incident cases and sufficient latency to account for the expected lengthy induction period for CLL.

Keywords: chronic lymphocytic leukaemia, aetiology, epidemiology.

Chronic lymphocytic leukaemia (CLL) is a common form of leukaemia; however, its aetiology remains largely unknown (Marti *et al*, 1997). It is strongly related to age and gender, and incidence and mortality rates vary substantially by ethnicity [Centers for Disease Control and Prevention (CDC), 2004; Parkin *et al*, 1997]. CLL has been associated with exposure to herbicides and with non-ionising radiation in some studies [Institute of Medicine of the National Academies (IOM), 2003]. The purpose of the current study was twofold: to describe in detail a specific study of CLL risk associated with workplace exposure to ionising radiation. We also reviewed findings from other recent studies on CLL risk associated with ionising and non-ionising radiation, particularly those that have emerged over the past 10 years.

Ionising radiation has been known as a cause of most forms of leukaemia for over 50 years, but it has not been found to be associated with CLL in several seminal studies of highly exposed populations. As a result, CLL is excluded in the US and the UK from programs to compensate workers for radiation exposures that were likely to have resulted in cancer (Wakeford, 2006). Moreover, authoritative organisations, such as the US National Research Council and the United Nations Scientific Committee on the Effects of Atomic Radiation, have concluded that there is little evidence that CLL is caused by ionising radiation [National Research Council (NRC), 2005; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2000].

The rationale for concluding that CLL is non-radiogenic has recently been challenged (Richardson *et al*, 2005) based on consideration of factors such as the low background incidence rate of CLL in some studies on which the presumption is based, and the anticipated long latency between its initiation and death from CLL. We conducted the present study within the context of a large nested case-control study of leukaemia

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among workers at four US Department of Energy (DOE) sites and a nuclear naval shipyard. The association between external exposure to ionising radiation and risk of non-CLL leukaemia has been described elsewhere (Schubauer-Berigan *et al*, 2007). This analysis specifically considers the association between ionising radiation from all workplace sources and CLL, while controlling for suspected sources of confounding.

Materials and methods

We conducted this study with the review and approval of the National Institute for Occupational Safety and Health (NIOSH) Human Subjects Review Board (protocol number HSRB-96-DSHEFS-10).

Cohort assembly

We identified eligible cohorts from 15 candidate sites within the US nuclear industry based on the availability of cohort and dosimetry data; whether the total cohort was of sufficient size to have generated at least 10 leukaemia deaths in previous investigations, and lack of substantial exposure to internal radiation. Based on these criteria, we excluded nine cohorts. Six existing cohorts met the inclusion criteria: four US DOE sites [Hanford, the Savannah River Site (SRS), Oak Ridge National Laboratory (ORNL), and Los Alamos National Laboratory (LANL) including the cohort of Zia Company workers originally studied separately] and the Portsmouth Naval Shipyard (PNS). We developed base cohorts for each of these sites from studies conducted by previous investigators (Rinsky *et al*, 1981; Galke *et al*, 1992; Gilbert *et al*, 1993; Wiggs *et al*, 1994; Frome *et al*, 1997; Cragle *et al*, 1999). We included workers of both genders and all races and ethnicities if they worked at the site for at least 30 d and were monitored for exposure to external ionising radiation. Characteristics of the 94 517 workers in the combined cohorts are given elsewhere (Table 1 of Schubauer-Berigan *et al*, 2007).

Case ascertainment

Previous investigators followed most cohorts through at least 1990. For this study, we extended follow-up through 1994 for Hanford and SRS, and through 1996 for PNS, using linkage to the US National Death Index. We obtained death certificates for each decedent identified at Hanford, SRS and PNS during this additional time period and coded them to the 9th revision of the International Classification of Diseases (ICD-9). Previous investigators had coded death certificates to other ICD revisions. We identified CLL cases using the relevant code from each of these ICD revisions (i.e., 204·1 for both ICD-8 and ICD-9), and by reviewing each death certificate with an indeterminate leukaemia subtype (e.g., ICD-6 and -7 codes 204·0, "lymphatic leukaemia"). We also used medical records obtained from site facilities to identify leukaemia subtype.

Table I. Characteristics of chronic lymphocytic leukaemia cases and age-matched controls.

	Cases	Controls	Total	Rate ratio (95% CI)
Number	43	172	215	
Male	39 (91%)	156 (91%)	195 (91%)	1·0
Female	4 (9%)	16 (9%)	20 (9%)	1·00 (0·28, 2·83)
White, non-Hispanic	40 (93%)	166 (97%)	206 (96%)	1·0
Non-white or Hispanic	3 (7%)	6 (3%)	9 (4%)	2·11 (0·42, 8·73)
Birth year <1912	15 (35%)	65 (38%)	80 (37%)	1·0
Birth year 1912–1921	19 (44%)	67 (39%)	86 (40%)	1·27 (0·55, 2·98)
Birth year ≥1922	9 (21%)	40 (23%)	49 (23%)	0·99 (0·35, 2·77)
Hire year <1947	13 (30%)	62 (36%)	75 (35%)	1·0
Hire year 1947–1952	18 (42%)	67 (39%)	85 (40%)	1·29 (0·59–2·86)
Hire year ≥1953	12 (28%)	43 (25%)	55 (26%)	1·34 (0·55–3·27)
Benzene + CCl_4 = 0	26 (60%)	114 (66%)	140 (65%)	1·0
0 < Benzene + CCl_4 < 200	8 (19%)	30 (17%)	38 (18%)	1·18 (0·47–2·74)
Benzene + CCl_4 ≥ 200	9 (21%)	28 (16%)	37 (17%)	1·37 (0·58–3·04)
Hanford	12 (28%)	72 (42%)	84 (39%)	1·0
ORNL	12 (28%)	26 (15%)	38 (18%)	3·21 (1·20–8·98)
LANL/Zia	5 (12%)	17 (10%)	22 (10%)	1·60 (0·45–5·13)
SRS	11 (26%)	29 (17%)	40 (19%)	2·52 (0·97–6·65)
PNS	3 (7%)	28 (16%)	31 (14%)	0·64 (0·14–2·19)
Never-smoked	17 (40%)	53 (31%)	70 (33%)	1·0
Ex-smokers*	16 (37%)	61 (35%)	77 (36%)	0·92 (0·42–2·03)
Current smokers	10 (23%)	58 (34%)	68 (32%)	0·45 (0·16–1·16)

ORNL, Oak Ridge National Laboratory; SRS, Savannah River Site; LANL, Los Alamos National Laboratory; PNS, Portsmouth Naval Shipyard.
*Last smoked at least 5 years before cutoff date.

Because non-underlying causes of death were not available for the LANL and Zia cohorts, we used only underlying cause of death to identify CLL cases.

Control selection

We selected four control subjects for each case, based on incidence density sampling using attained age as the time scale (Beaumont *et al*, 1989). In this method, we matched controls to cases on age by requiring controls to have been hired at a younger age than the death age of the case, to have worked at least 30 d, and to have survived to an older age than the case. Incidence density sampling from the risk set within a nested cohort assures that the odds ratio (OR) estimates the rate ratio that would be obtained in a full cohort study. This required truncating exposures for each control at the date (the ''cutoff date'') of his or her reaching the age at death of the matched case, minus any lag being evaluated.

Exposure assessment

The diverse characteristics of ionising radiation exposures and wide variety of dosimetry practices among facilities and over time necessitated facility- and job-specific adjustments to individual reported exposures to ensure comparability. Therefore, we developed methods to account for recognised biases in the measurement processes that arise from exposure to heterogeneous radiation fields, calibration methods, dosimeter design, dosimeter energy response, and geometry of the critical organ (Daniels & Schubauer-Berigan, 2005; Daniels & Yiin, 2006; Daniels *et al*, 2006). We then normalised exposure variables to the individual tissue equivalent dose, where the specified tissue is active bone marrow, to account for differences in radiation types.

Radiation exposures were quantified as equivalent dose to the hematopoietic bone marrow, primarily resulting from x-ray, gamma, and neutron irradiation by workplace sources external to the body. We assessed external radiation dose for each case and control using available site records. Methods used to estimate individual external doses from gamma and x-ray exposures below the detection limit are described elsewhere (Daniels *et al*, 2004; Daniels & Schubauer-Berigan, 2005; Daniels & Yiin, 2006). We estimated doses from work-related medical x-ray examinations using a computer code developed by the Finnish Centre for Radiation and Nuclear Safety (Servomaa & Tapiovaara, 1998). We reviewed worker medical records and site records to determine x-ray examination frequencies, techniques, and equipment specifications (Anderson & Daniels, 2006). Although overall exposures to internally deposited radionuclides were expected to be small in these cohorts, we evaluated potential systemic deposition (as estimated by urinary excretion) and subsequent dose to the bone marrow from plutonium, given its use in study facilities (other than PNS) and high dose per unit intake relative to other internal agents, as described elsewhere (Daniels *et al*, 2006; Schubauer-Berigan *et al*, 2007). Finally, some workers received internal whole body exposures to tritium-bearing compounds, which were assessed using similar methods.

For neutrons, radiation weighting factors were applied based on energy using International Commission on Radiological Protection (ICRP) 60 values (ICRP, 1992), and a radiation weighting factor was applied of 20 for plutonium dose. We lagged bone marrow doses by discounting any exposure received during the ten years before the cases and controls reached the age at death of the case. A ten-year lag period was selected to account for the longer preclinical and clinical course of CLL (Richardson *et al*, 2005).

We evaluated benzene and carbon tetrachloride as potential confounders based on their known or suspected association with other forms of leukaemia and their expected differential exposure among workers in the study. We obtained detailed work history information for each worker and used available data and historical records to identify potential exposure activities and histories for benzene and carbon tetrachloride at each site. We used a job-exposure matrix to link study subjects with exposure activities, and developed an algorithm to calculate cumulative exposure scores for both benzene and carbon tetrachloride for each study subject.

$$\text{Cumulative Score} = \sum L_{i,j,k} * D * F$$

Where L = level, F = frequency, D = duration, i = compound, j = worker, k = year.

We assigned study subjects linked with an exposure activity to one of five categories based on work history and exposure activity history information. For each worker category within each exposure activity, we estimated qualitative values for exposure level, frequency and duration based on available information regarding the activity at the site and our professional judgment. We assigned numerical values to these qualitative exposure level estimates, based on expert judgment, to allow calculation of exposure scores for both, as described elsewhere (Schubauer-Berigan *et al*, 2007).

We assembled histories of tobacco use, available for 58% of the workers, from worksite medical records; however, we found sufficient information to determine each worker's cigarette smoking status as of his or her cutoff date for only 45% of the workers in the study. We classified workers as (i) never-smoked, (ii) ex-smokers or (iii) current smokers. We defined ex-smokers as workers who smoked cigarettes but quit more than 5 years prior to their cutoff date. We defined current cigarette smokers as workers who were smoking cigarettes or who quit smoking five or fewer years before their cutoff date. For workers with insufficient smoking information, we imputed smoking status based on the socioeconomic status associated with first job title after Yiin *et al* (2005) refined to reflect average smoking histories for a given job from survey data collected between the 1950s and 1980s [e.g., Hrubec *et al* (1992)]. We validated these assignments using the relationship between job titles and smoking history for workers

with complete information. The surrogate methods demonstrated fair diagnostic discrimination, and accurately identified 61% of the smokers and 64% of non-smokers.

We obtained information on race and Hispanic ethnicity for study subjects using workplace medical records, supplemented with linkage to the Hispanic surname registry for men with unknown ethnicity. We collapsed race and ethnicity data for analysis into two categories: ''white, non-Hispanic'' and ''non-white or white Hispanic'' due to the very small percentage of non-white or Hispanic study subjects (4%).

Statistical analysis

We calculated descriptive statistics for the cohort and for case-control study subjects using SAS ver 8.0 (SAS Institute, Inc., Cary, NC, USA). Main analyses were based on external dose (excluding plutonium). We conducted epidemiological analyses using conditional logistic regression (PECAN module of Epicure) (Preston *et al*, 1993), analyzing risk conditionally on the matched sets. We evaluated a linear excess relative rate (ERR) model for most analyses. This model is commonly used to analyse radiological cohorts (NRC, 2005) and facilitates comparisons to other studies.

We used a loglinear model for some analyses to permit estimation of the lower confidence limit. We also reported results comparing risks among workers exposed above 10 mSv to those among workers exposed at lower levels. To examine further the shape of the dose-response analyses, other loglinear categorical analyses were conducted with dose cutpoints selected *a priori* at 1, 10, 50 and 100 mSv. We estimated two-sided 95% confidence intervals (CI) for β_i parameters using profile likelihood methods (Preston *et al*, 1993). The analysis approach for evaluating potential confounders and effect modifiers (i.e., sex, race/ethnicity, facility of longest employment, smoking status, tertiles of birth cohort and hire year, and exposure to benzene and carbon tetrachloride) is as described elsewhere (Schubauer-Berigan *et al*, 2007). Sensitivity analyses (all planned *a priori*) were conducted by (i) excluding workers receiving more than 100 mSv (to determine whether any observed results were driven by high-dose workers) (ii) including plutonium dose, and (iii) evaluating risk in time windows of exposure before the cutoff date.

Results

Descriptive analyses

Most study subjects were non-Hispanic white and male (Table I). Most workers had no exposure to benzene or carbon tetrachloride, and most were either current or ex-smokers. Gamma, beta and x-ray radiation resulted in 95–97% of the total bone marrow equivalent dose for study subjects. Mean cumulative external bone marrow doses were lower among cases than controls, although increasing the lag period decreased this difference, and confidence intervals (not shown) were wide. Median doses were 11·4 mSv among cases and 9·0 among controls with a ten-year lag applied.

The CLL mortality rate ratio did not vary by sex (Table I). Workers who were non-white or Hispanic had approximately double the mortality rate of CLL compared to whites. Little variability was seen in the CLL rate ratio by birth cohort. Workers hired later had slight but non-significant elevations in the CLL rate ratio. The age-adjusted CLL mortality rates were approximately threefold higher among Oak Ridge and SRS workers compared to workers at Hanford. Workers at PNS had lower rates compared to Hanford workers, although confidence intervals were quite wide (Table I).

The CLL mortality rate among smokers was estimated to be about half that among those that never-smoked, and the rate ratio was similar when considering only the study subjects with non-imputed smoking data (OR = 0·74, 0·15–3·77 with 18 cases). We observed a slight positive trend of rate ratio with increasing benzene and carbon tetrachloride exposure, although the confidence intervals were wide in the exposed categories (Table I).

Risks associated with radiation exposures: main analysis

Workers who received doses of 10 mSv or more had a non-significantly higher CLL mortality rate than those who received doses below that level [relative risk (RR) = 1·36; 95% CI: 0·69, 2·70]. Workers with higher estimated plutonium deposition showed slightly higher CLL rates than workers with no plutonium deposition, although the confidence intervals widely overlapped unity (Table II). CLL mortality rates were non-significantly higher among workers receiving doses between 10 and 100 mSv compared to those receiving less than 1 mSv. Rate ratios in the group receiving 1–10 mSv were not elevated, and no CLL cases were observed among workers receiving 100 mSv or more (Table II). Rate ratio estimates in external dose categories were not greatly affected by adjustment for potential confounding factors (data not shown). No effect modification was apparent in the categorical analyses. The linear ERR was estimated at −0·020 per 10 mSv (Table II) and did not vary with the inclusion of potential confounders. This negative trend was heavily influenced by the lack of observed CLL cases at or above 100 mSv.

Risks associated with radiation exposures: sensitivity analysis

Excluding workers who received more than 100 mSv resulted in non-significantly positive OR estimates for CLL mortality. The ERR per 10 mSv was 0·20 (95% CI: −0·036, 0·96), adjusted for smoking, the only confounder. No evidence of radiation effect modification was observed by sex ($P = 0{\cdot}62$), birth cohort ($P = 0{\cdot}18$), hire year ($P = 0{\cdot}53$), smoking ($P = 0{\cdot}88$), facility ($P = 0{\cdot}83$), or benzene and carbon tetrachloride exposure ($P = 0{\cdot}52$). A highly significant apparent interaction

Table II. Dosimetry-related characteristics and chronic lymphocytic leukaemia rate ratios.

Characteristic	Cases	Controls	Total	Rate ratios (95% CI)
Pu excreta level (x) categories				
Unmonitored	21 (49%)	93 (54%)	114 (53%)	1·0
Monitored, with x < 1·7 mBq/d	18 (42%)	63 (37%)	81 (38%)	1·23 (0·60, 2·52)
1·7 mBq/d≤ x < 17 mBq/d	4 (9%)	11 (6%)	15 (7%)	1·57 (0·40, 5·21)
≥17 mBq/d	0	5 (3%)	5 (2%)	0 (NC, 2·29)
Total external dose, unadjusted for confounders				
Ten-year lag: 0–<1 mSv	6 (14%)	29 (17%)	35 (16%)	1·0
1–<10 mSv	14 (33%)	63 (37%)	77 (36%)	1·09 (0·39, 3·35)
10–<50 mSv	18 (42%)	55 (32%)	73 (34%)	1·63 (0·62, 4·84)
50–<100 mSv	5 (12%)	13 (8%)	18 (8%)	2·00 (0·49, 8·05)
≥100 mSv	0 (0%)	12 (7%)	12 (6%)	0 (NC, 1·02)
Loglinear model: OR at 10 mSv (95% CI)				0·96 (0·86, 1·03)
Linear ERR model: ERR per 10 mSv (95% CI)				−0·020 (NC, 0·14)

OR, odds ratio; ERR, excess relative rate; NC, not calculable.

Table III. Effect on smoking-adjusted radiation-related chronic lymphocytic leukaemia rate ratio of excluding high-dose workers, including plutonium dose, excluding neutron dose from total external dose, and breaking external dose into time windows.

Dose category	Rate ratio (95% CI), including all workers	Rate ratio (95% CI), excluding workers >100 mSv
Total external dose: 0–<1 mSv	1·00	1·00
1–<10 mSv	1·09 (0·38, 3·42)	1·09 (0·38, 3·42)
10–<50 mSv	1·65 (0·61, 4·99)	1·65 (0·61, 4·99)
50–<100 mSv	2·55 (0·59, 11·0)	2·55 (0·59, 11·0)
≥100 mSv	0 (NC, 1·01)	–
Linear model: ERR per 10 mSv:	−0·02 (NC, 0·16)	0·20 (−0·035, 0·96)
Including Pu dose: 0–<1 mSv	1·00	1·00
1–<10 mSv	1·09 (0·39, 3·40)	1·10 (0·39, 3·42)
10–<50 mSv	1·68 (0·62, 5·10)	1·68 (0·62, 5·08)
50–<100 mSv	1·83 (0·38, 8·45)	2·28 (0·52, 9·81)
≥100 mSv	0·38 (0·02, 2·52)	–
Linear model: ERR per 10 mSv:	−0·020 (NC, 0·14)	0·16 (−0·044, 0·83)
Photon & tritium dose only: 0–<1 mGy	1·00	1·00
1–<10 mGy	1·08 (0·38, 3·37)	1·08 (0·38, 3·37)
10–<50 mGy	1·68 (0·62, 5·09)	1·68 (0·62, 5·09)
50–<100 mGy	2·57 (0·59, 11·1)	2·57 (0·59, 11·1)
≥100 mGy	0 (NC, 1·00)	–
Linear model: ERR per 10 mGy:	−0·020 (NC, 0·15)	0·19 (−0·046, 0·95)
Linear model: ERR per 10 mSv (95% CI):		
Time window category: 0–<2 years	−0·29 (<0, 0·75)	−0·28 (<0, 1·25)
2–<5 years	0·18 (<0, 4·1)	−0·12 (<0, NC)
5–<10 years	−0·090 (<0, 0·82)	−0·14 (<0, 0.44)
10–<20 years	−0·037 (<0, 3·5)	0·30 (<0, 1·6)
≥20 years	−0·018 (<0, 0·13)	0.26 (<0, 1·6)

ERR, Excess relative rate; NC, not calculable.

was observed with race/ethnicity ($P = 0·002$), but the risk coefficients were uninterpretable due to the very small number of non-white or Hispanic workers in the study.

Incorporating plutonium bone marrow dose had little effect on smoking-adjusted CLL rate ratio estimates (Table III). Excess rate ratios were consistently below zero for analyses including all workers and were non-significantly greater than zero for analyses excluding workers who received 100 mSv or more. Similarly, removing neutron dose had little effect on the estimated rate ratios: ERR per 10 mSv was estimated at 0·19 (95% CI: −0·046, 0·95) for analyses excluding the higher-dose workers and adjusting for smoking.

Splitting external radiation dose into time windows prior to the cutoff date led to very different rate ratio estimates; however, confidence intervals were wide for ERR estimates per

unit of dose (Table III). For analyses in which workers exposed to 100 mSv or more were excluded, ERR estimates were negative for time periods of less than 10 years before the end of risk and positive for time periods of greater than or equal to 10 years, although confidence intervals all overlapped zero. The time window pattern for analyses including all workers detected a positive association for the exposure period of 2–5 years before age at death of the case and negative estimates for other time periods.

Discussion

This study of workers at four DOE facilities and one nuclear naval shipyard, one of the largest to explicitly examine the association between CLL and ionising radiation exposure, observed suggestive evidence of an association between radiation dose and CLL at doses below 100 mSv, but not at higher doses. The impact of excluding workers who received more than 100 mSv is clearly important in interpreting this study's findings: the smoking-adjusted ERR per 10 mSv of total external photon dose was estimated to be negative [−0·020 (95% CI: not calculable, 0·16)] when high-dose workers were included, and was positive [0·20 (95% CI: −0·035, 0·96)] when they were excluded. At the mean cumulative dose of about 20 mSv, the ERR excluding high-dose workers is 0·40 (95% CI: −0·070, 1·9).

The time window analysis among the study group, when high-dose workers were excluded, produces ERR estimates that are very similar for exposures received 10 years or more before the age at risk, suggesting that a lag period of ten years was appropriate for this group. This finding, if confirmed in other studies, may suggest that radiation acts as a CLL promoter, given the very slow clinical course and progression of this disease.

We excluded workers receiving more than 100 mSv in sensitivity analyses because it is frequently of interest to understand whether observed risk elevations are influenced by workers receiving higher exposures (e.g., Cardis *et al*, 2007). We did not anticipate that the exclusion of high-dose workers would lead to an elevation in ERR estimates per unit of dose, but it is of note that this was also observed in the results for non-CLL leukaemia in this same population (Schubauer-Berigan *et al*, 2007). Studies of exposures in occupational cohorts, including nuclear workers, frequently show attenuation of risk at the highest exposure categories (Stayner *et al*, 2003). This has been attributed to a variety of potential phenomena, including the healthy worker survivor effect, exposure misclassification that is greater for workers receiving high as compared to low exposures, confounding by other risk factors, or saturation of enzyme-mediated carcinogenic pathways (Stayner *et al*, 2003). The healthy worker survivor effect is unlikely to explain this attenuation for cancers not related to lifestyle factors (Stayner *et al*, 2003). Overall exposure misclassification cannot be ruled out as a source of risk attenuation.

Damage process saturation is unlikely for non-CLL leukaemias, as many studies of radiation-exposed cohorts have detected effects for non-CLL leukaemia at exposures many times higher than 100 mSv (Ron, 2003; Preston *et al*, 2004; Krestinina *et al*, 2005). However, the possibility that the association of CLL with radiation may be a predominantly low-dose phenomenon cannot be excluded, as CLL has not typically been observed to be elevated in high-dose studies, and relatively few low-dose studies have explicitly examined CLL risk. Random variability must also be considered a likely explanation for the variability in rate ratios as doses increase.

Apart from radiation, few factors were found to be associated with CLL in this study. Unexpectedly, background CLL rates did not differ among male and female workers. Age-adjusted US CLL mortality rates for white males were, on average, about double that for white females between 1979 and 2002 (CDC, 2004). In this study, although confidence intervals were wide, cases were found to be about half as likely as controls to be current smokers. Cigarette smoking has not generally been found to be associated with CLL [e.g., Schollkopf *et al* (2005) found a negative association of borderline significance]; a more likely explanation in this study was that the five-year lag used to consider a worker an ex-smoker was too short for a disease with a slow progression. Cases may have been more likely to quit smoking more than 5 years before death as a result of their disease.

Strengths of the present study include the size of the population, the inclusion of all workers, and the characterisation of exposures to potential confounders, such as workplace solvents and smoking. Further strengths include the ability to adjust for suspected sources of bias in radiation dosimetry measurement data. Limitations of the study include its lack of incident CLL cases; probable poor diagnostic discrimination from lymphomas and (possibly) other leukaemias; overall low power; the few exposed person-years at long latencies, particularly in the high-dose groups; and the inability to explore certain potential risk factors, such as electromagnetic field (EMF) exposures. Although occupational exposures to EMF were initially considered, insufficient information existed to provide meaningful estimates for workers at the sites. An additional limitation is the limited follow-up period (through just 1990 for some cohorts). For the four cohorts for which complete death certificate information is available (Hanford, SRS, PNS and ORNL), 13 non-underlying CLLs were identified (as compared to 38 underlying CLLs), suggesting that this limitation may have affected study precision.

Review of recent studies of ionising and non-ionising radiation

Ionising radiation

Environmentally exposed populations Studies of Japanese atomic bomb survivors have been fundamental to the establishment of radiation exposure limits for workers and

the public. Among the most recent studies of Japanese atomic bomb survivors, all risk models for leukaemia were based on mortality, not incidence. With follow-up until 2000, CLL comprised just six of 296 leukaemia deaths (Preston *et al*, 2004), which is not unexpected given the low background rate of CLL in Japan. Radiation-related risk estimates do not vary with exclusion of CLL. Thus, this study does not appear particularly informative about radiation-related risk of CLL.

Residents of the Techa River region in the former Soviet Union who were exposed to high external radiation levels from contamination due to weapons manufacture (Krestinina *et al.*, 2005) showed no significant association of CLL risk with radiation exposures (ERR = 0·005 per 10 mSv, $P > 0·5$). However, with only 11 cases, a young age distribution and relatively high loss to follow-up, the study is currently not very informative for CLL risk.

In the US, the most recent analyses of populations exposed to fallout from nuclear weapons testing identified 238 CLLs by death certificates and registries (Stevens *et al*, 1990). A weak positive trend was observed, of the same magnitude as other leukaemias and all leukaemias combined. However, only six cases were exposed to >6 mGy. Removal of hairy-cell leukaemias reduced the observed trend for CLL.

Medically and occupationally exposed populations As recently reviewed by Silver *et al* (2007), few studies of populations exposed medically to ionising radiation have shown significantly increased risk of CLL, although non-significant increases were associated with increased follow-up time in many of the studies. However, as described in that review, such studies have a number of serious limitations, such as the follow-up time at which CLL risk has been considered, lack of quantitative exposure information for the study groups, and reporting bias.

This reporting bias has been seen also in occupational radiation studies. Generally, studies reporting CLL risk in radiation workers have not found consistent evidence of radiogenicity (Silver *et al*, 2007). The most recent results of occupational studies of ionising radiation have also provided somewhat equivocal results (Table IV). Neither the 15-country study of nuclear workers (Cardis *et al*, 2007) nor a study of workers at the Mayak facility in the former Soviet Union (Shilnikova *et al*, 2003) found an association between CLL and ionising radiation; however, a significant association was observed among Czech uranium miners (Rericha *et al*, 2006) and workers at the Rocketdyne facility in the US (Boice *et al*, 2006). In the former study, radon bone marrow dose was highly correlated with gamma exposure (also significantly associated with CLL in the study). In addition, attenuation of CLL risk was described to occur in the highest dose group. An incidence-based study of radiological technologists found a non-significant positive association with length of time holding patients during x-rays (Linet *et al*, 2005).

Table IV. Results of recent occupational cohort studies.

	ERR per 10 mSv (95% CI; *n*)	
Study	CLL	Non-CLL
Mortality-based		
15-country (Cardis *et al*, 2007)	<0 (*n* = 47), lag2	0·019 (<0, 0·071, 196)
NIOSH LCCS (This study & Schubauer-Berigan *et al*, 2007)	−0·02 (<0, 0·14; 43), lag10 0·20 (−0·036, 0·96)<100 mSv	0·014 (−0·010, 0·076, 206) 0·068 (−0·029, 0·24) <100 mSv
Rocketdyne (Boice *et al*, 2006)	SMR = 2·06 (*n* = 7), lag2 Dose trend $P < 0·01$, 0·21*	SMR = 1·17 (*n* = 18) Dose trend $P = 0·18$
Chernobyl (Konogorov *et al*, 2000)	0·013, (−0·063, 0·089; 41 all leuk combined)	0·16 (−0·25, 0·56)
Mayak workers (Shilnikova *et al*, 2003)	No association, *n* = 11, $P > 0·5$	9·9 (4·5, 21·2; 66)†
Incidence-based		
Uranium miners (Rericha *et al*, 2006)	RR (110 WLM: 3 WLM) 1·98 (1·10, 3·59; 53)	1·86 (0·79, 4·36; 25)‡
Radiological technologists (Linet *et al*, 2005)	RR (held patients for x-ray ≥50x vs. <50x) 1·4 (0·6, 3·5; 22)	2·6 (1·3, 5·4; 39)

CLL, chronic lymphocytic leukaemia; ERR, excess relative rate; RR, relative risk; SMR, standardized mortality ratio; WLM, working level months.

*Adjusted for other covariates.

†Estimate is per 10 mGy, and 90% CI are reported.

‡Includes only myeloid leukaemias.

Non-ionising radiation

Both ultraviolet and EMF radiation have been evaluated as potential causes of CLL. Smedby *et al* (2005) found no trend in CLL risk with sun sensitivity among 752 CLL and small-cell lymphomas in Denmark and Sweden. However, significant negative trends were observed with three important measures of sun exposure: sunbathing, ''sun vacations'' and sunburn in youth. A positive risk of CLL was observed among those with skin cancer diagnosed >1 year earlier.

A large number of studies have been conducted regarding the risk of childhood leukaemia (primarily acute lymphoblastic leukaemia) from exposure to extremely low frequency (ELF) EMF radiation. A recent pooled case-control study (Schuz *et al*, 2007) found a monotonic increase in childhood leukaemia with increasing night-time exposure to ELF EMF. However, CLL is virtually non-existent among children. Evidence of the association between EMF and CLL derives largely from studies of railway workers. A weak dose-response association was observed between magnetic fields and CLL, among both men and women, in the largest of these studies (Floderus *et al*, 1993, 1999). Among Swiss railway workers, ELF EMF was observed to be associated with myeloid, but not lymphatic, leukaemia (Roosli *et al*, 2007). Interpretation of results for CLL is difficult given the small number of cases ($n = 36$, none were among the workers receiving higher exposures), and lack of differentiation of acute from chronic leukaemia types. At higher magnetic field frequencies (e.g., 50 Hz), studies of adults living near high-voltage power lines have provided some evidence of increased risk of CLL. Tynes and Haldorsen (2003) observed a monotonic increase in the incidence rate of CLL with increased 50-Hz field exposure (P for trend = 0·06, $n = 85$) among adults in Norway. The magnitude of risk increased when exposure received more than 10 years before case diagnosis was included (P for trend = 0·03). A large study of UK electric power workers (Harrington *et al*, 2001), however, found no increase in CLL mortality associated with increased exposure (P for trend >0·5, $n = 39$). Other studies of EMF have been limited by small numbers of CLLs (e.g., Minder & Pfluger, 2001), a lack of explicit consideration of CLL, or non-reporting of results by leukaemia subtype.

Limitations of existing studies

Few studies have found CLL to be significantly associated with ionising radiation exposure, as described in a recent review (Silver *et al*, 2007). Criticisms of existing studies include inadequate follow-up time for a disease with a long preclinical phase, lack of consideration of sufficient latency between exposure and CLL mortality, the lack of diagnostic specificity for CLL, and a strong underreporting bias (Richardson *et al*, 2005). Most studies are based on death certificate reports or, at best, cancer registries. ICD-9 and −10 codes do not give information to differentiate B-cell from T-cell types. Underattribution to CLL is likely to occur because of long progression (often to other infectious or malignant disease) and death at older ages when accuracy is poor. Diagnostic discrimination between it and other leukaemias and small-cell lymphoma is probably poor, particularly for older studies. The mechanism of leukaemogenesis [inhibition in apoptosis in addition to monoclonal proliferation (Chiorazzi *et al*, 2005)] for CLL differs from other leukaemias, making long latency likely. However, studies frequently use short dose lags for CLL (e.g., 2 years). As shown in our case-control study, a latency of 10 years was more consistent with the observed excess risk of leukaemia between 10 and 100 mSv. Studies with primarily internal exposure show suggestive elevations in risk. However, the appropriate target organ to use in these studies is unclear.

Lastly, the paradigm that CLL is not caused by ionising radiation inhibits its evaluation in many epidemiological studies, particularly with extended follow-up. Evidence of CLL's radiogenicity is sometimes interpreted as evidence against causal attribution for other leukaemias (e.g., Boice *et al*, 1996, 2006), rather than being considered on its own merits.

Conclusions

The nested case-control study described here, one of the largest to specifically evaluate the risk of chronic lymphocytic leukaemia among nuclear workers, did not find a consistent association between radiation and CLL. CLL rates showed some evidence of elevation at external doses between 10 and 100 mSv, but not at exposures greater than 100 mSv. Recent studies of uranium miners in Europe (Rericha *et al*, 2006) and of workers at the Rocketdyne facility (Boice *et al*, 2006) have shown evidence of possible elevations in risk. To be informative, future studies of CLL incidence will be required in large populations with a wider range of doses, careful case definition, and increased follow-up to elucidate the association between CLL and ionising radiation. The use of biomarkers that may lead to CLL (such as monoclonal B-cell lymphocytosis) as study outcomes may further increase the power of future studies to investigate aetiologic factors related to CLL. However, the feasibility of such biomarkers in large epidemiological studies, and their lack of validation (e.g., sensitivity and specificity) render their use of questionable practical significance.

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