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Ionizing Radiation and Risk of Chronic Lymphocytic Leukemia in the 15-Country Study of Nuclear Industry Workers

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Abstract

In contrast to other types of leukemia, chronic lymphocytic leukemia (CLL) has long been regarded as non-radiogenic, i.e. not caused by ionizing radiation. However, the justification for this view has been challenged. We therefore report on the relationship between CLL mortality and external ionizing radiation dose within the 15-country nuclear workers cohort study. The analyses included, in seven countries with CLL deaths, a total of 295,963 workers with more than 4.5 million person-years of follow-up and an average cumulative bone marrow dose of 15 mSv; there were 65 CLL deaths in this cohort. The relative risk (RR) at an occupational dose of 100 mSv compared to 0 mSv was 0.84 (95% CI 0.39, 1.48) under the assumption of a 10-year exposure lag. Analyses of longer lag periods showed little variation in the RR, but they included very small numbers of cases with relatively high doses. In conclusion, the largest nuclear workers cohort study to date finds little evidence for an association between low doses of external ionizing radiation and CLL mortality. This study had little power due to low doses, short follow-up periods, and uncertainties in CLL ascertainment from death certificates; an extended follow-up of the cohorts is merited and would ideally include incident cancer cases.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a common type of leukemia with a largely unknown etiology (1). Although there is strong evidence that other types of leukemia are linked with ionizing radiation, CLL has long been regarded as non-radiogenic, i.e. not caused by ionizing radiation (2). This has led occupational compensation programs in some countries (for example in the UK and the U.S.) to assign CLL a zero probability of causation, meaning that, in those countries, radiation-exposed workers with CLL cannot claim compensation (3, 4).

The classification of CLL as non-radiogenic is based mainly on evidence from studies of medically exposed populations, which have found radiation associations primarily for non-CLL leukemia (2). Studies of the Japanese atomic bomb survivors have not been informative, because CLL is very rare in this population (5). Although the evidence for CLL radiogenicity is clearly not as strong as for other forms of leukemia, whether CLL is associated with radiation remains a topic of debate. The clinical characteristics of CLL, including its long latency and asymptomatic period, higher prevalence at older age, mild symptoms and low fatality rate, have led to underascertainment of CLL on death certificates and thus to low power in studies of mortality (1, 6, 7). Further, its classification as non-radiogenic has led many studies to exclude CLL from analyses and/or reports. For these reasons, the justification for the assignment of CLL as non-radiogenic has been challenged (6–9).

The 15-country study of nuclear industry workers is the largest study of nuclear industry workers to date, and it provides direct evidence concerning the effects of low-dose occupational exposure to ionizing radiation. This study has recently published its radiation-related cancer mortality risk estimates (10). To contribute to the current debate on CLL-radiogenicity, this paper presents detailed analyses of radiation-related CLL risk.

MATERIAL AND METHODS

The 15-country study is a retrospective cohort study of mortality among nuclear workers. Detailed methods, including the follow-up approach used in each participating cohort, have been published elsewhere (11). The main study population was defined as workers who had been employed in at least one of the study facilities for at least 1 year, who had been monitored for external radiation exposure, and whose doses consisted predominantly of higher-energy photon radiation (X and γ rays in the range 100–3000 keV). For each worker monitored for external radiation exposure, individual annual radiation doses were obtained from facility records and/or national dose registries. Doses to specific organs were derived by dividing the recorded doses by organ dose bias factors developed in a study of errors in doses (12). In the CLL analyses, doses to the active bone marrow were used. All doses are expressed in terms of equivalent dose in sievert (Sv).

Cohorts included in the analyses of CLL were all those with at least one CLL death (Table 1). The analyses used linear and log-linear models. The linear relative risk Poisson regression model assumed the relative risk (RR) to be of the form $1 + \beta Z$, where Z is the

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cumulative dose in Sv, and β is the excess relative risk (ERR) per Sv (10). In the CLL analyses, the MLE of this model was on the lower boundary of β defined by 1/max(dose). We therefore focus on log-linear Poisson models, in which the RR is assumed to be of the form exp(βZ). Likelihood-based confidence intervals are presented. Cumulative doses were lagged by 10 years to allow for the long latent period of CLL and in analogy with our analyses of other cancer outcomes (10). Sensitivity analyses were also conducted using other lag times (2, 5, 15, 20 and 25 years). Estimates of the ERR and RR were stratified by sex, age and calendar period (both in 5-year categories), facility, duration of employment (<10 years, ≥10 years), and socio-economic status (SES) (10). Analyses of separate cohorts were conducted only for cohorts with more than five CLL deaths; the remaining cohorts were combined.

The outcome was mortality from CLL as underlying or associated cause of death (ICD 8 and 9 code 204.1). ICD revisions in use before around 1970 (ICD 6, 7) did not distinguish CLL with a separate code. Cohorts that had leukemia deaths before 1970 (U.S. and UK) recoded all early deaths to ICD 8 or 9 by review of the death certificates. It was judged important to include associated causes, because CLL patients often die from causes other than CLL, so CLL may not be given as the underlying cause of death on the death certificate (6). Information on associated causes of death was collected by four countries (France, Sweden, UK and U.S.) contributing 84% of workers in the study.

The 15-country study was approved by the IARC Ethical Review Committee and by the relevant ethics committees of the participating countries. The study did not involve contact with study subjects.

RESULTS

The cohorts included in the analysis of CLL comprised 295,963 workers, followed up for a total of 4,530,294 person years, with an average cumulative bone marrow dose of 14.7 mSv (Table 1). In total, there were 65 deaths with CLL as underlying (N = 47) or associated (N = 18) cause within these cohorts. Most cohorts contributed very few CLL cases. The cohorts of the UK (N = 19) and of Hanford (N = 12) and Idaho National Laboratory (INL) (N = 14) in the U.S. contributed the majority of cases.

In all cohorts combined, there was no evidence of an association between radiation dose and CLL risk: The ERR per Sv was on the lower boundary of β (= −0.86) defined by 1/max(dose), while the log-linear model showed an RR at 100 mSv of 0.84 (95% CI 0.39, 1.48). In the analyses by cohort, CLL risk estimates were nonsignificantly reduced in the UK and Hanford cohorts and nonsignificantly increased in INL (RR at 100 mSv = 1.13, 95% CI 0.11, 2.88), Oak Ridge National Laboratory (ORNL) (RR = 1.96, 95% CI 0.01, 17.4), and the other cohorts combined (RR = 1.23, 95% CI 0.30, 2.79) (Table 2). Confidence intervals were very wide, however, and there was no evidence for heterogeneity in risk estimates between the cohorts (P = 0.73 in the log-linear model). Risk estimates per unit radiation dose did not vary substantially by attained age (P = 0.48): <60 years (N = 15) RR = 0.81, 95% CI 0.14, 2.10; 60–70 years (N = 21) RR = 1.12, 95% CI 0.52, 1.89; and ≥70 years (N = 29) RR = 0.39, 95% CI 0.05, 1.25).

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For all cohorts combined, relative risk estimates decreased with increasing lag times, from 0.91 at 100 mSv with a lag of 2 years to 0.81 with a lag of 20 years and 0.43 with a lag of 25 years (Table 2). Similarly, in most individual cohorts, longer lag times resulted in lower risk estimates (not shown). Longer lag periods resulted in lower cumulative doses, so the findings for the longer lag periods are based on very small numbers of deaths in higher dose categories. For example, analyses using a 20-year lag included only three CLL cases with a dose of 50 mSv or more, one at Hanford and two in the combined small cohorts. Under a 20-year lag, central estimates of the relative risk were above one at Hanford (RR at 100 mSv = 1.26, 95% CI 0.04, 9.36) and in the combined small cohorts (RR = 2.77, 95% CI 0.53, 8.26) but below one in the other cohorts; confidence intervals were invariably wide and included unity.

DISCUSSION

This study finds little evidence that mortality from chronic lymphocytic leukemia is related to external ionizing radiation dose, although we were not able to exclude a risk similar to that observed for other leukemia types due to the wide confidence intervals. These findings are consistent with results from previous large-scale nuclear workers studies that have examined CLL: the 3-country study (13) and the second analysis of the National Registry for Radiation Workers of the United Kingdom (14). The overall risk estimate is also similar to that published previously by the 15-country study, based on underlying causes of death only and using a 2-year lag (RR at 100 mSv = 0.90) (10). General strengths and weaknesses of the 15-country study have been discussed in great detail elsewhere (10, 11, 15). A main limitation in the analysis of other cancer types was the inability to adjust for individual smoking habits (10), but confounding by smoking is not a major concern in CLL analyses, because there is little evidence that smoking is a risk factor for CLL (16). For CLL, potential confounders include chemical exposures such as solvents (17) and other risk factors such as race (18), but no information on such factors was available. A recent case-control study (including workers at Hanford, ORNL and three sites not included in the 15-country study) that adjusted for exposure to benzene and carbon tetrachloride found no evidence of confounding by these solvents (8).

Despite its size, this study had little power for several reasons. Most nuclear workers received very low doses of radiation; hence it is difficult to detect small increases in risk. CLL is a slow-progressing cancer with a comparatively long latency and asymptomatic period; a long lag period between exposure and effect (i.e. mortality from CLL) is therefore appropriate, but our analyses with longer lag periods included very few CLL deaths with higher doses. Nevertheless, increasing the lag period from 10 years to 15, 20 and 25 years did not change the overall results substantially. It may be of interest that the analyses using a 20-year lag period showed increased risk estimates, although far from statistically significant, in the only cohorts with any CLL deaths at cumulative doses over 50 mSv. However, these analyses should be interpreted with great caution because they are based on very few deaths. Analyses of the effects of age at risk and time since exposure on radiation-related CLL risk were not attempted due to low power. The follow-up periods in most cohorts included in this study were relatively short (average 13 years), and the majority of

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workers were comparatively young (average 46 years) at the end of the follow-up. Further follow-up of these populations may be useful to improve power.

Ascertainment of CLL through death certification is open to outcome misclassification and underascertainment, which may in turn reduce the power of this study. CLL is characterized by a long asymptomatic period, mild symptoms, and low fatality rate. CLL patients often die at older age from competing causes of death, and thus CLL may be not be stated as cause of death on the death certificate (6). Inconsistencies in the diagnosis and classification of CLL have long existed due to analogies with lymphocytic lymphoma (18, 19), leading to further possible inaccuracies in the case ascertainment. It should further be noted that CLL could not be distinguished in the early ICD revisions. In this study, cohorts with leukemia deaths before this time recoded early deaths to later ICD revisions, but some misdiagnosis may have occurred; we feel that this probably does not affect a large proportion of cases, because there were few leukemia deaths before 1970 ($N = 35$), and if we apply the post-1970 proportion of CLL cases out of all leukemia cases (22%) to the pre-1970 cases, no more than three CLL cases are estimated to be missing due to misdiagnosis.

In conclusion, the largest nuclear workers cohort study to date provides little evidence for an association between CLL mortality and external ionizing radiation at low doses. However, the power of the study is low due to the low doses, short follow-up periods in most cohorts, and uncertainties in CLL ascertainment from death certificates. Tentative suggestions of higher radiation-related CLL risk with long lag periods in some of the cohorts merit further exploration in an extended follow-up of the nuclear workers cohorts, ideally including cancer incidence follow-up.

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TABLE 1

Description of the Relevant[a] Study Cohorts and Numbers of Deaths from CLL

	Number of facilities	Earliest year of start of operations	Follow-up period	Number of workers	Person-years	Average bone marrow dose (mSv)	Deaths from CLL[b]
Australia	1	1959	1972–1998	877	12.110	4.4	3
Canada	4	1944	1956–1994	38,736	473,880	15.5	4
Finland	3	1960	1971–1997	6,782	90,517	5.8	I
France CEA COGEMA	9	1946	1968–1994	14,796	224,370	3.1	1
France EDF	22	1956	1968–1994	21,510	241.391	12.7	1
Sweden	6	1954	1954–1996	16,347	220.501	13.7	1
UK	32	1946	1955–1992	87,322	1,370,101	15.4	19
U.S. Hanford	1	1944	1944–1986	29,332	678,833	18.1	12
U.S. INL	1	1949	1960–1996	25,570	505.236	7.6	14
U.S. NPP	15	1960	1979–1997	49,346	576.682	20.9	3
U.S. ORNL	1	1943	1943–1984	5,345	136,673	12.0	6
Total	95	—	—	295,963	4.530.294	14.7	65

Note. Abbreviations used: CEA-COGEMA: Commissariat à l'Energie Atomique - Compagnie Générale des Matières Nucléaires; EDF: Electricité de France; NPP: Nuclear Power Plants; INL: Idaho National Laboratory; ORNL: Oak Ridge National Laboratory.

[a] Cohorts with one or more CLL case.

[b] Underlying and associated causes of death.

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TABLE 2

Risk Estimates per Unit Radiation Dose for CLL, Overall, by Cohort, and by Lag Period

		Linear model		Log -linear model	
	No. of CLL cases	**ERR/Sv**	**95% CI**	**RR at 100 mSv[a]**	**95% CI**
Overall (lag 10 years)					
All cohorts	65	<0[b]	—	0.84	0.39 1.48
By cohort (lag 10 years)					
UK	19	<0	—	0.55	0.10 1.52
U.S.-Hanford	12	<0	—	0.67	0.04 2.24
U.S.-INL	14	6.43	<0 115.3	1.13	0.11 2.88
U.S.-ORNL	6	nd[c]	—	1.96	0.01 17.4
Other cohorts combined[d]	14	4.88	<0 98.1	1.23	0.30 2.79
P for heterogeneity (*df* = 4)		*P* = nd		*P* = 0.73	
By lag period (all cohorts)	No. with dose ≥50 mSv				
2 years	10	<0	—	0.91	0.50 1.39
5 years	10	<0	—	0.87	0.45 1.41
10 years	8	<0	—	0.84	0.39 1.48
15 years	5	<0	—	0.85	0.35 1.65
20 years	3	<0	—	0.81	0.26 1.86
25 years	0	<0	—	0.43	0.05 1.74

[a] Compared to baseline category of 0 mSv.

[b] <0: Central risk estimate or lower confidence bound cannot be estimated as it is on boundary of parameter space (— 1/maxdose).

[c] nd: not determined: the model did not converge.

[d] Cohorts with less than 5 CLL cases combined: Australia. Canada, Finland, France, Sweden, U.S. NPP.