

# Chronic lymphocytic leukemia radiogenicity: a systematic review

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## Abstract

**Objective** Chronic lymphocytic leukemia (CLL) is generally considered to be non-radiogenic and is excluded from several programs that compensate workers for illnesses resulting from occupational exposures. Questions about whether this exclusion is justified prompted a Congressional mandate to the National Institute for Occupational Safety and Health (NIOSH) to, further, examine the radiogenicity of CLL. This study revisits the question of CLL radiogenicity by examining epidemiologic evidence from occupationally and medically-exposed populations.

**Methods** A systematic review of radiation-exposed cohorts was conducted to investigate the association between radiation and CLL. Exploratory power calculations for a pooled occupational study were performed to examine the feasibility of assessing CLL radiogenicity epidemiologically.

**Results** There is a bias against reporting CLL results, because of the disease's presumed non-radiogenicity. In medical cohort studies that provide risk estimates for CLL, risk is elevated, though non-significantly, in almost all studies with more than 15 years average follow-up. The results of occupational studies are less consistent.

**Conclusions** Studies with adequate follow-up time and power are needed to better understand CLL radiogenicity. Power analyses show that a pooled study might detect risk

on the order of radiation induced non-CLL leukemia, but is unlikely to detect smaller risks.

**Keywords** Chronic lymphocytic leukemia · Ionizing radiation · Radiogenicity

## Introduction

The etiology of chronic lymphocytic leukemia (CLL) is largely unknown. Studies have demonstrated the involvement of immune system components and genetic abnormalities in the pathogenesis of CLL [1, 2]. Observation of trisomy 12, abnormalities in chromosome 13q14 [3], familial clustering [4], and the phenomenon of anticipation [5] in CLL patients suggest the involvement of multiple genetic pathways.

The role of environmental exposures, such as ionizing radiation and chemicals, in CLL etiology is unclear. Several studies have noted elevations of CLL among farmers [6–8], suggesting increased CLL risk due to exposure to herbicides or pesticides [9]. Exposure to ionizing radiation has also been examined as a potential risk factor for CLL. Since no increases in CLL were observed among the Life Span Study cohort of atomic bomb survivors [10] or among large cohorts treated therapeutically with radiation [11–13], the disease is generally considered non-radiogenic [14].

The US Energy Employees Occupational Illness Compensation Act (EEOICPA) considers CLL non-radiogenic; in fact, CLL is the only cancer assigned a causation probability of zero under EEOICPA [15]. The decision to exclude CLL from compensation stemmed from a lack of evidence for CLL radiogenicity in medically exposed cohorts and in large occupational studies. CLL is also excluded from other compensation programs, including the

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Radiation Exposure Compensation Act (RECA) [16], which compensates uranium millers and miners and those exposed to fallout from atmospheric nuclear tests. In contrast, other “non-radiogenic” diseases, like prostate cancer and hairy cell leukemia (a malignancy similar to CLL), are compensated under EEOICPA.

It has recently been recognized that the presumption of non-radiogenicity was based, in part, on studies of atomic bomb survivors, a population with a low background rate of the disease [17]. This observation, together with concerns about discrepancies in compensation practices, prompted a Congressional mandate to the National Institute for Occupational Safety and Health (NIOSH) to further investigate the radiogenicity of CLL.

A meta-analysis of the available literature was attempted, but was not feasible due to heterogeneity in study populations and exposures, a lack of explicit reporting of CLL risk estimates, and differences in reporting measures. Instead, a systematic review was conducted to assess the epidemiological evidence pertinent to CLL radiogenicity. In addition, a power analysis was conducted to evaluate the potential of a pooled study of radiation-exposed workers to contribute to the understanding of CLL radiogenicity.

In order to maximize the probability of adequate dosimetry and minimize uncontrolled confounding, this review was restricted to studies of persons exposed to radiation occupationally or as medical patients. The review excluded environmentally exposed populations, such as communities living near nuclear facilities.

Pertinent medically exposed populations include patients treated with therapeutic X-rays or brachytherapy for malignant or benign conditions, given diagnostic X-rays, exposed to Thorotrast, or receiving diagnostic or therapeutic Iodine-131 ( $^{131}\text{I}$ ) for thyroid conditions. Occupational cohorts included in the review comprise nuclear facility workers, radiologists and radiologic technicians, airline crews exposed to cosmic radiation, nuclear test participants, and cleanup workers following nuclear accidents, such as Chernobyl.

## Materials and methods

### Systematic review

Pubmed and Excerpta Medical (EMBASE) databases were searched through early 2005, with no language restriction, to identify quantitative epidemiological studies of populations exposed to radiation occupationally or during medical treatment or diagnosis. Studies were required to provide risk estimates based on standardized populations or internal comparison groups. Controlling for attained age was required, as CLL is highly correlated with age [18]. Case

series, studies of ecologic design, and studies with only proportionate mortality ratio results were excluded.

The initial search used Medical Subject Headings (MeSH) entry terms for “leukemia” and “radiation.” The search was narrowed to target epidemiology studies by requiring a term from the following set: “epidemiology,” “cohort,” “case–control,” “relative risk” and “odds ratio,” “risk ratio,” “standard mortality ratio,” “standard incidence ratio,” “standard rate ratio,” “excess relative risk,” “observed to expected” and “O:E.” The refined search yielded 2,840 unique citations. Abstract scans resulted in the exclusion of many articles. Nearly 900 articles were not epidemiological studies of occupationally or medically-exposed populations. As CLL primarily affects adults, nearly 800 studies focusing on childhood exposures or outcomes were excluded. Smaller numbers of articles were excluded because they reported only on non-CLL leukemia subtypes, studied Asian populations (while CLL is the most prevalent adult leukemia in Western populations [19] it accounts for only 3–5% of leukemia among Asian populations [20]), or followed patients treated for primary lung cancer (because of low survivability) or primary hematopoietic malignancies (due to diagnostic similarity and possible shared etiology with CLL). Populations exposed only to non-ionizing or ultra-violet radiations were excluded, as well.

Following the abstract scan, 293 articles were retained for full-text examination. Additional articles were identified via searches of dissertation abstracts (UMI ProQuest) and of a NIOSH library holding published and unpublished reports from epidemiologic studies of Department of Energy workers. After applying exclusion criteria to the full-text articles, 210 articles remained, where articles did not report CLL-specific results, but suggested that such analyses had been performed, authors were contacted with requests for CLL results or pertinent data files. In most cases these requests were not successful.

A number of medical studies reported CLL results, but failed to differentiate results by chemotherapy or by radiotherapy status. Where these studies are informative (i.e., no CLL deaths or cases observed despite a mixture of therapies) they are discussed. Where updates of specific occupational or medical populations exist, this review presents results from the latest update, except where an earlier study provided CLL risk results and the update did not, or where one study gave mortality results and another, incidence results. The original CLL results from study cohorts later included in pooled analyses are discussed.

### Power analysis

Power calculations were completed to examine the feasibility of evaluating the relation between external radiation

and CLL through a pooled cohort mortality study of radiation-monitored workers. Egret<sup>®</sup> Siz software [21] was used to perform the analyses. A Poisson model was assumed where external dose was categorized into four groups: 0–10 millisievert (mSv), 10–50 mSv, 50–100 mSv, and >100 mSv. These cutpoints were chosen to be consistent with studies on which the dose distribution was based [Los Alamos National Laboratory (LANL) and the Portsmouth Naval Shipyard (PNS)]. Age and sex, known risk factors for CLL, were also considered. In specifications for age and sex sampling fractions by dose, basic assumptions were that younger workers have lower cumulative doses than older workers, and that the ratio of males to females increases with dose category.

Expected relative risks (RRs) for CLL for each variable were specified in the model. The RRs for CLL at each level of external dose were derived from the National Academies' Biological Effects of Ionizing Radiation (BEIR) V model [14] for non-CLL leukemia. Also, a more conservative analysis was run using RRs consistent with lymphoma (excess relative risk (ERR) per Sv = 0.178), obtained from the Centers for Disease Control and Prevention (CDC) and National Cancer Institute (NCI) working group tables [22]. Midpoints of each dose category were used to calculate the RR; the highest category used a dose midpoint of 150 mSv (leukemia: RR at >100 mSv = 1.63, NHL: RR at >100 mSv = 1.02). CLL RRs for age were estimated from CDC Wonder [23] age-specific CLL rates. The RR comparing females to males was assumed to be 0.5, based on the literature [24]. An annual case rate for CLL among the baseline stratum (females, age 25–44) of 2.0735 per 10,000,000 was assumed, again based on CLL mortality rates available from CDC Wonder.

Person-year (PY) extrapolations were performed for selected cohorts (based on data availability) to complement the power analysis. These cohorts included the US Idaho National Laboratory (INL) cohort [25] and the US

Multi-Site Leukemia Case Control Study (LCCS) cohort (Schubauer-Berigan et al., in review), which consists of the contributing cohorts LANL, Hanford, Savannah River Site (SRS), PNS, and Oak Ridge National Laboratory. Required demographic information included age structure of the cohort and age at hire, in order to determine PY begin dates. Datasets were available in-house for the US cohorts. Published data on the age distribution and average date of hire were available for the United Kingdom (UK) National Registry of Radiation Workers (NRRW) [26], Canada's National Dose Registry [27], and the Russian National Medical Dosimetric Registry of Chernobyl workers [28]; thus these cohorts were included in the analysis. The Life Table Analysis System software [29] and country-specific life tables (and state, age, and race specific, where available) were used to estimate the expected number of deaths, and resulting person years, over several time intervals. Deaths were assumed to occur in the middle of the interval. Persons still anticipated to be alive contributed PY over the entire interval. In addition, a 15 year lagged PY extrapolation was performed on the INL and LCCS cohorts (data were not available for the UK and Canadian cohorts); person-years and deaths which occurred during the first 15 years of follow-up were ignored.

## Results

### Search results

Only 46 studies (23 medical and 23 occupational) reported risk estimates for CLL, and some of these had overlapping populations (Table 1). In addition, eight medical and eight occupational studies reporting zero CLL cases were considered informative and retained. Studies reporting results both for leukemia and leukemia excluding CLL were retained, although these results are less informative than CLL-specific analyses. The

**Table 1** Medical and occupational studies by result type

Results provided	Medical studies	Occupational studies
Risk estimate for CLL	23 (1 <sup>a</sup> )	23 (6 <sup>a</sup> )
CLL results but failure to separate RT+ and RT– treatment, or RT and chemotherapy patients	12	N/A
Risk estimates for all leukemia combined and leukemia excluding CLL	0	24 (6 <sup>a</sup> )
0 CLL observed	8	8
Only all leukemia combined; observed number CLL is reported and >0	18	10
Only all leukemia combined; number CLL not reported <sup>b</sup>	19	58
Excludes CLL a priori <sup>b</sup>	3	4
Total	83	127

<sup>a</sup> Met inclusion criteria, superseded by more recent update (counted in total)

<sup>b</sup> Used only to identify studies that might have been informative had CLL been reported

remaining studies provided no CLL risk estimates (report only number of CLL observed).

A number of medical studies had clearly performed pertinent subtype analyses, but did not explicitly report CLL risk estimates, likely because the disease was regarded as non-radiogenic. For example, a study of endometrial cancer patients included CLL as a negative control to detect ascertainment bias [30]. Other authors excluded CLL from the primary or secondary analyses, stating that it is presumed to be non-radiogenic [31], reported only that CLL risk does not appear to be increased without presenting risk estimates [32], or simply mentioned that results were similar for CLL and non-CLL [33]. Other studies did not differentiate by chemotherapy status; those with positive findings [34] are difficult to interpret, as either radiation or chemotherapy could be responsible.

Like the medical studies, some occupational studies performed CLL specific analyses, but did not report CLL risk estimates [35]. Other studies reported a summary of risk estimate for CLL, but excluded CLL from dose–response or time since exposure analyses because the summary estimate was not elevated [36, 37]. However, recent results from a study of radiation workers at PNS demonstrate that a summary risk estimate at or below expectation does not preclude a significant dose–response in internal analyses [38].

Some occupational studies reported risk estimates for all leukemia, but only the number of CLL cases, which is often small. Of occupational studies reporting the number of leukemias found but no subtype data, a few, including analyses of US Department of Energy (DOE) workers at the K-25 site (unpublished report, Dupree et al., 1994) and the X-10 and Y-12 sites [39], French Atomic energy workers [40], and US radiologic technologists [41], reported more than 40 leukemia cases each and might have had sufficient CLL cases to provide useful dose–response or time since exposure results.

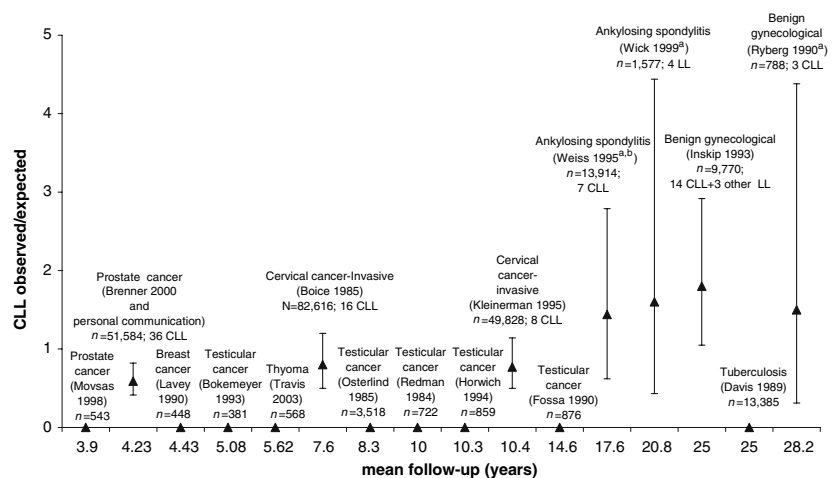
In contrast, some studies had valid ascertainment or risk estimation issues that precluded reporting CLL-specific risk estimates. In a study of  $^{131}\text{I}$  exposed-patients, Hall et al. report that coding for leukemia did not permit differentiation between acute and chronic leukemia [42]. Darby et al., in their study of women treated by X-rays for metropathia hemorrhagica, reported that risk estimates by subtype were not available for the target population during the study period [43], although they noted that no evidence of an excess of CLL was found in the population. Similarly, in studies of airline workers, Blettner et al. and Zeeb et al. [44, 45] reported only all leukemia, because subtypes could not consistently be determined from death certificates. These legitimate reporting issues may play a role in decisions by other researchers to report risk estimates only for all leukemia combined.

## Study results

### Medical studies

*External radiation and brachytherapy for malignant conditions, non-malignant conditions, and diagnostic purposes* The medical cohort studies tend to exclude CLL from dose–response or time since exposure analyses, but often provide average follow-up time for the cohort. While dose–response or time since exposure analyses would be preferable, average follow-up is also informative, as studies with longer average follow-up are more likely to have a greater percentage of person years at risk with adequate latency. Examination of medical cohort studies [46–61] shows a pattern of risk estimates for irradiated patients below 1.00 with average follow-up of less than 15 years (Fig. 1). With longer follow-up time ( $\geq 15$  years), all studies have point estimates greater than 1.00 for irradiated patients, with the exception of one low-dose

**Fig. 1** Medical cohort studies and clinical trials: results by follow-up time. Outcome is CLL mortality except where indicated. Point estimate ( $\blacktriangle$ ); <sup>a</sup> incidence studies; <sup>b</sup> RT + O/E = 1.44, RT– O/E = 2.0; *n* = number of irradiated study subjects; # of CLL in irradiated pts. Results from Brenner et al. [47] were supplemented by personal communication from Brenner to Silver received 1/14/05



[mean absorbed dose to active bone marrow = 0.09 gray (Gy)] study of tuberculosis patients [60] which found no CLL deaths among the 6,285 exposed cohort members. However, confidence intervals for the majority of these positive results span the null, due in part to the scarcity of CLL cases.

The RRs comparing patients treated with radiotherapy (RT+) to non-irradiated patients (RT−) are not presented in all of these studies, so Fig. 1 displays risk estimates for the irradiated patients. For several studies, the overall risk estimates for irradiated patients were lower than those for their non-irradiated counterparts. These include studies of cervical cancer patients by Boice et al. [51] and by Kleinerman et al. [55], as well as a study of ankylosing spondylitis by Weiss et al. [57]. Follow-up was less than 11 years for the first two studies, but the study of ankylosing spondylitis patients [57] had average follow-up greater than 15 years. Interestingly, the Kleinerman study provided O:E data by time since treatment as well; the results for time periods >20 years since treatment showed a greater O:E ratio for irradiated patients than for their non-irradiated counterparts. This result demonstrates that summary estimates can be misleading, particularly when over influenced by patients with short follow-up (and thus by large numbers of person years in cells with little latency and thus, if latency is long, little risk).

While the studies of testicular cancer presented in Fig. 1 had no CLL cases with fewer than 15 years average follow-up, two other studies did report CLL cases following treatment for this illness, although they failed to provide risk estimates [62, 63]. In addition, Hay et al. studied 517 Scottish testicular cancer patients followed an average of 15.4 years [64] and found two leukemia cases, both CLL, for an all-leukemia O:E ratio of 3.91. No CLL-specific risk estimate is provided, but the CLL risk estimate would also be positive for this study, which had longer follow-up than other testicular cancer research.

Some medical cohort studies did not report mean follow-up time and are, therefore, excluded from Fig. 1. In a study of benign lesions of the locomotor system (ankylosing spondylitis, arthritis, and other conditions) among Swedish patients diagnosed between 1950 and 1964 and followed through 1988, Damber et al. [65] reported a standardized incidence ratio (SIR) for CLL of 1.07 (95% CI = 0.80, 1.41;  $n = 50$ ). Follow-up time was at least 24 years for surviving patients. In contrast, in an incidence study of Danish patients with in situ and invasive cervical cancer [66], the RR for CLL in patients treated by radiotherapy ( $n = 7$ ) versus non-irradiated patients remained constant at 0.9 for the follow-up period of over 20 years (average follow-up is not given). A clinical trial for ovarian cancer [67] found no incident lymphatic leukemia cases in the radiation-treated group. Average follow-up was not

given by treatment type; median follow-up for the entire cohort was 13.5 years.

Results of six cohort studies that give CLL results but fail to separate risk estimates by chemotherapy status are generally consistent with those shown in Fig. 1. Most have mean follow-up ranging from 3.2 years to 10.2 years; four [68–71] reported either no CLL cases or CLL risk below expectation. While Curtis et al. [72] found a non-significant excess of CLL with average follow-up of 4.6 years, both CLL cases occurred at >10 years after initial ovarian cancer diagnosis. An expansion of this cohort, with average follow-up of 4.1 years, found an overall deficit of CLL in ovarian cancer patients regardless of chemotherapy status [69]. One exception is a study of testicular cancer [34]; with an average follow-up of eight years an elevated O:E of 3.5 was observed, based on only one case.

Case-control studies of second malignancies following radiotherapy rarely report CLL results. A study of uterine cancer [73], with average follow-up of 8.2 years and control for alkylating agents, found a matched RR for CLL incidence of 0.90 (95% CI = 0.4, 1.9,  $n = 57$ ). A breast cancer study [31] with an average interval between breast cancer and leukemia diagnoses of 12 years, found a non-significant increased relative risk of subsequent CLL diagnosis of 1.84 (90% CI = 0.5, 6.7,  $n = 10$ ). CLL was excluded from dose-response analyses; the authors note that the disease is not believed to be radiogenic. The authors restricted the treatment period to 1972 or earlier to reduce the likelihood that chemotherapy was used. Another cervical cancer study, which used CLL as a negative check [11], reported results for this outcome near expectation (incident CLL RR = 1.03, 90% CI = 0.3, 3.9,  $n = 52$ ). Finally, a study comparing estimated radiation dose from diagnostic X-rays in CLL cases versus controls found a deficit in risk that was statistically significant with a five-year lag; however, no longer lag periods were evaluated [74].

Other case-control studies of second primaries and diagnostic procedures have methodological drawbacks, such a study basing exposure on number of self-and proxy-reported X-rays which found a reporting bias [75]. A study of radiotherapy for various primaries [76] had no dosimetry data, and only evaluated incident CLL risk as a check against study bias.

### *Thorotrast*

The CLL risk estimates for patients exposed to Thorotrast are available from a multi-national cohort study by Travis et al. [77] and a German study by van Kaick et al. [78]. The multinational study saw a sizable but non-significant increase of CLL among Swedish and Danish Thorotrast



patients (RR = 9.3, 95% CI = 0.9, 356.6,  $n = 6$ ). The Danish portion of the cohort was studied previously [79]; an RR of 6.00 (95% CI = 0.77, 121.06,  $n = 4$ ) was found with follow-up exceeding 20 years. In contrast, van Kaick et al. [78] found a risk ratio of 0.8 (3 CLL cases) when comparing Thorotrast-exposed patients with controls, after 31 years mean follow-up, but this estimate did not adjust for age, sex, or calendar year. Finally, dos Santos Silva's study of 2,427 Portuguese Thorotrast-exposed patients and 2,558 unexposed patients [80] found no CLL deaths at 15.3 years average follow-up in systemically exposed patients and 38.2 years in locally exposed patients.

### <sup>131</sup>I

Of epidemiologic research involving patients treated with I131, two major studies with follow-up greater than 20 years present CLL risk estimates. Hall et al. studied Swedish patients given <sup>131</sup>I between 1950 and 1975, with a mean follow-up of 21 years [42]; results differed by the indication for treatment. While the overall SIR for CLL was 1.08 ( $n = 65$ , 95% CI = 0.84, 1.38,  $n = 65$ ), risk estimates were below expectation for hyperthyroidism but significantly elevated for treatment of thyroid cancer, with a slight, non-significant elevation for diagnostic administration of <sup>131</sup>I. SIR results for the entire group of patients were below expectation from two to nine years after exposure, but showed non-significant elevations with longer intervals since exposure. Relative risk estimates generally rose with administered dose category, adjusted for sex, age at exposure, and calendar year, and attained statistical significance for doses at or above 100 mGy for CLL but not for non-CLL.

The other major <sup>131</sup>I study, by Ron et al., examined treatment of 35,593 hyperthyroid patients, of whom about 65% were treated with <sup>131</sup>I treated 1946–1964 in the US, with a mean follow-up of 21 years [81]. The CLL SMR for patients with Graves' disease (PY = 368,934) treated by <sup>131</sup>I dose was 1.33 ( $n = 19$ ), while there were no deaths in a smaller group (PY = 13,088) so treated for toxic nodular goiter. Relative risk for CLL decreased with administered activity, with an ERR of  $-0.008 \text{ mCi}^{-1}$  administered activity. Three smaller studies with average follow-up of 10 years or less report finding no CLL cases [82–84].

### Occupational studies

*Nuclear facility workers—external exposure* Nuclear facility studies report CLL risk in a variety of ways, complicating comparison between the studies. One of the three occupational studies to present ERR results for CLL

explicitly is the International Agency for Research on Cancer (IARC) three-country mortality study of nuclear workers [85], that combined cohorts from the US (Hanford, Oak Ridge National Laboratory, and Rocky Flats), UK (Atomic Weapons Establishment (AWE), Atomic Energy Authority's Sellafield facility) and Canada (Atomic Energy of Canada Ltd.). The combined cohort included 95,673 workers with average follow-up of 22 years. There were 147 leukemia deaths, with 27 from CLL. For CLL, the ERR per Sv was estimated to be  $-0.95$  (90% CI =  $<0$ , 9.4); however, only a two-year lag was employed. Results for leukemia excluding CLL exhibited heterogeneity by facility, but no facility-specific analyses for CLL were presented. An update of the multinational study, analyzing approximately 400,000 monitored workers from 15 countries, has been published recently and reported results for leukemia excluding CLL [86]. The manuscript describing overall and facility-specific CLL analyses for this updated cohort was not available at the time of this analysis.

A mortality study at INL [formerly known as the Idaho National Engineering and Environmental Laboratory (INEEL)], which followed 63,561 workers for an average of 21.2 years [25], also found a negative ERR ( $-1.45$  per Sv, SE =  $2.80 \times 10^{-3}$ ,  $n = 21$ ) with a seven-year lag for CLL. Various lag assumptions, up to 20 years, were tested in the analysis of CLL; the maximum risk for non-CLL leukemias was observed with a seven-year lag, but the CLL risk did not vary by lag. No CLL deaths were seen in the highest dose group ( $\geq 100$  mSv). The CLL ERR was much lower than the ERR for leukemia other than CLL.

The LCCS included cases and controls from a number of nuclear facilities (SRS, Hanford, PNS, ORNL, LANL, and Zia) and had the methodological advantage of controlling for potential chemical confounders, including chemical exposures. The study included 43 CLL deaths; interestingly, none occurred in the highest dose group (workers receiving at least 100 mSv external dose). With a 10-year lag, the ERR was negative (ERR per Sv =  $-2$ , 95% CI  $<0$ , 14); however, when workers in the highest dose category were excluded, the estimate was positive, though non-significant (ERR per Sv = 20, 95% CI  $-3.6$ , 96) [Schubauer-Berigan et al. in review].

A number of occupational studies report ERR results for leukemia and for leukemia excluding CLL [26, 27, 87–92] (Fig. 2). In theory, if CLL has no relation with radiation exposure, the risk estimates for leukemia excluding CLL would be higher than those for all leukemia. Several studies of the US and Canadian nuclear power cohorts, report ERR results for leukemia and leukemia excluding CLL. The effects of excluding CLL differ depending on whether incidence or mortality is studied and the specific subset of workers studied. For example, in the Canadian studies, while the Sont mortality study [87] of the Canadian

**Table 2** Occupational studies with ERR results for leukemia and leukemia excluding CLL

Study (study type)	Population	Average follow-up (years)	Lag (years) subset	Leukemia ERR (CI) per Sv; # cases	Leukemia-CLL ERR (CI) per Sv; # cases
Sont et al. [87] (i, co)	Canada, National Dose Registry <i>n</i> = 191,333	14	2 (males) 2 (males & females)	5.9 (90% 0.3, 22.7); 68 5.4 (90% 0.2, 20.0); 98	2.7 (90% <0, 18.8); 45 Not given
Zablotska et al. [88] (m, co)	Canada, National Dose Registry—IARC subcohort <i>n</i> = 45,468	13.4	2	18.9 (95% -2.08, 138); 22	52.5 (95% 0.2, 291); 18
Ashmore et al. [27] (m, co)	Canada, National Dose Registry <i>n</i> = 206,620	13.8	2 (males) 2 (females)	0.2 (90% -4.7, 5.0); 56 -0.2 (90% -19.4, 19.1); 46	0.4 (90% -4.9, 5.7); 26 -0.2 (90% -20.3, 20.0); 23
Howe et al. [89] (m, co)	US Nuclear Power <i>N</i> = 53,698	13	2	8.89 (95% -1.04, 36.4); 29	5.67 (95% -2.56, 30.4); 26
Muirhead et al. [26] (m, co)	UK NRRW <i>n</i> = 124,743	16.5	2	1.20 (90% -0.68, 4.61); 117	2.55 (90% -0.032, 7.16); 91
McGeoghegan and Binks [90] (m, co)	Springfield Plant-UK <i>n</i> = 19,454	24.6	2	-1.96 (90% <-1.97, 4.84); 22	-1.96 (90% <-2.00, 9.78); 14
Kubale et al. [91] (m, ca)	PNS Nested in cohort of 37,853 workers	26.3	2	23 (95% 3, 88); 115 (34 radiation-monitored)	23 (95% 3, 88); 101 (31 radiation-monitored)
Konogorov et al. [92] (m, ca)	Chernobyl <i>N</i> = 162,684	NG; max = 9	2	1.33 (95% -6.25, 8.90) per Gy; 41	15.59 (95% -24.9, 56.1) per Gy; 28

I = incidence; m = mortality; ca = case-control study; co = cohort study

National Dose Registry, as mentioned, shows a decreased risk when CLL is excluded, the Ashmore et al. [27] mortality study of this group showed a very slight increase. The Zablotska mortality study [88] of the IARC subset of the Registry, showed a strong increase in risk from 18.9 per Sv (95% CI  $-2.08$ , 138) to 52.5 per Sv (95% CI 0.21, 291) when CLL was excluded.

Several mortality studies present O:E ratios or standardized rate ratios (SRR) by external dose category, along with trend tests for CLL (Hanford [36], Mound [93], LANL [94], and an unpublished study by Cragle et al. of Fernald workers). Only the Hanford study [36] had more than four CLL deaths. None of the 6 CLL deaths was observed at or above 100 mSv; overall CLL trend statistics were  $-0.45$  for a two-year lag and  $-0.34$  for a 10-year lag. However, these tests tend to be less negative than those reported for leukemia excluding CLL ( $-0.81$  and  $-0.85$  respectively).

Other studies reporting trend tests or risk estimates for leukemia and leukemia excluding CLL include the United Kingdom Atomic Energy Authority (UKAEA) mortality study [95], the Sellafield mortality and morbidity study [96], and an unpublished study by Dupree-Ellis et al. of mortality in Mallinckrodt workers. Only the UKAEA study had more than four CLL cases. The study of 26,395 workers found 24 CLL deaths and a slightly higher SMR for leukemia (SMR = 1.18, 95% CI 0.91, 1.51) than for leukemia excluding CLL (SMR = 1.07, 95% CI 0.76, 1.46) in radiation workers.

A study of the SRS [97] examined CLL as an explicit outcome. However, only SMR analyses were performed and the numbers are quite small. An excess of CLL deaths was observed among white male cohort members compared to the US population, with an SMR of 1.57 (95% CI = 0.67, 2.8,  $n = 8$ ). The CLL SMR for black males was even higher at 5.01 (95% CI = 0.95, 12.3,  $n = 3$ ).

Some studies of nuclear facility workers report zero CLL cases or deaths arising despite adequate follow-up. Unfortunately, most do not provide the expected number of CLL cases, precluding assessment of whether CLLs are in deficit or close to expectation [98]. While a study by Koshurnikova et al. [99] of mortality in workers at the Mayak facility found no incident CLL cases in workers employed 1948–1972 followed through 1989, an expansion and update of this cohort through 1997 [35] found 11 CLL deaths among 77 deaths from leukemia but no effects of external or internal dose on CLL risk ( $p > 0.5$ ).

#### *Chernobyl cleanup workers, liquidators, and emergency workers*

Three large populations of Chernobyl cleanup workers came from areas that are now Russia, the Ukraine, and

Belarus; a smaller group of workers came from Estonia. Many of these workers received substantial dose over a relatively short period of time. Dose varied by year, dropping particularly after 1988. Boice and Holm [100] estimated that for 300,000 workers 1986–1987 working within the 30 km zone the average dose was approximately 100 mGy, with perhaps 4% of the workers receiving  $>250$  mGy.

A study of 162,684 emergency workers from the Russian Federation [92] found 41 incident leukemia cases, of which 28 were CLL (results were provided for leukemia and leukemia excluding CLL). Mean age of entry into the 30 km zone was 34.0, and mean dose was 105 mGy. As shown in Table 2, the ERR for leukemia was lower than that for leukemia excluding CLL; maximum follow-up was less than 10 years.

The smaller group of 4,742 Estonian clean up workers had experienced no incident leukemia cases by end of follow-up in 1993; however, average follow-up of the cohort was only six years [101]. The mean dose to these workers is not known, but appears to have been less than that accrued by other cleanup worker groups [102].

#### *Uranium miners*

With respect to occupational radon exposure, one large study of underground miners performed a collaborative analysis of data from 11 international cohorts [103]. The study provided risk estimates for leukemia and leukemia excluding CLL by time since first employment and by cumulative working-level months (WLM). Of 69 leukemia deaths, 33 were from CLL. In early follow-up ( $<10$  years since first employment) the SMR was higher for leukemia (1.93, 95% CI 1.19, 2.95,  $n = 21$ ) than for leukemia excluding CLL (1.28, 95% CI 0.51, 2.64,  $n = 7$ ). However, for the time period of 10 years or more since first employment, the SMR for leukemia was 0.99 (95% CI 0.73, 1.31,  $n = 48$ ), while that for leukemia excluding CLL was 1.08 (95% CI 0.73, 1.55,  $n = 29$ ). In contrast, an incidence study of Czech uranium miners by Rericha et al. [104] showed positive risk estimates for CLL, with 53 cases. The study used an unusual design involving case-subcohort comparisons with inverse empirical sampling. In internal comparisons of workers at the 80th vs. 20th percentile of cumulative exposure, the CLL RR was significantly elevated at 1.98 (95% CI 1.10, 3.59).

#### *Radiologic technologists and radiologists*

A study of CLL mortality among radiologists registered before 1936 found an excess risk of borderline significance



(O:E = 2.86, one-sided  $p = 0.06$ , with expectation derived from population of the same social class), although only two cases were found [105]. The most recent mortality update of the US radiologic technologists [41] excluded CLL; however, a previous study of this population [106] did analyze CLL mortality. Out of the 103 leukemia deaths observed, 18 were due to CLL. The RRs showed no relation with the number of years certified, but were generally higher those certified before 1940, when doses were presumably higher. No significant increase of CLL was found.

A cancer incidence study [107] in a subset of this population found an SIR of 1.18 (95% CI = 0.72, 1.83,  $n = 24$ ). The SIR for all leukemia was 1.09 (95% CI = 0.87, 1.32,  $n = 75$ ). However, these estimates were based on a combination of death records and questionnaire data (weighted for non-response), with not all self-reported diagnoses confirmed by records. In a 2005 study by Linet et al. [108], internal comparisons were performed on a subset of the incidence study cohort. In this study, with 23 incident CLL cases, none of the proxy factors for radiation dose (years worked as a technologist, by calendar time and age; specific work practices) had statistically significant relative risks estimates or showed categorical estimates suggestive of a dose–response.

#### Airline pilots and cabin crew

Two multinational studies of European pilots have overlapping populations [109, 110]. A cancer incidence study of 10,211 airline pilots by Pukkala et al. [109] found differences in risk by time since first employment. The overall CLL SIR was 1.03 (95% CI = 0.28, 2.64;  $n = 4$ ), but all CLL cases occurred at >20 years since first employment, where four CLL cases were observed versus 3.2 expected for an SIR of 1.31 (95% CI = 0.36, 3.36). In dose analyses, elevations were restricted to two intermediate dose categories, with SIRs of 2.46 (95% CI = 0.06, 13.7;  $n = 1$ ) in the 3–9.99 mSv and 2.64 (95% CI = 0.32, 9.52;  $n = 2$ ) in the 10–19.9 mSv dose categories. The other multinational study [110] used mortality as an endpoint, and reported

SMRs for leukemia and leukemia excluding CLL by dose category. Findings were similar to those of Pukkala et al. (risk estimates increased when CLL was excluded except in the intermediate dose category of 15–25 mSv).

#### Nuclear weapons test participants

Studies conducted by Thaul et al. [37] and Muirhead et al. [111, 112] followed participants in nuclear test series conducted in the 1950s and 1960s. Both compared mortality and cancer incidence among test participants to the same outcomes in groups of non-participant veterans (Table 3). While Thaul et al. reported SMRs below expectation, both studies found non-significantly higher relative risks for test participants than for their non-participant counterparts. Thaul et al. reported better ascertainment among the exposed, potentially biasing the results. In the Muirhead studies, all CLL deaths occurred at least 10 years after first test participation, but most were in the lowest dose categories.

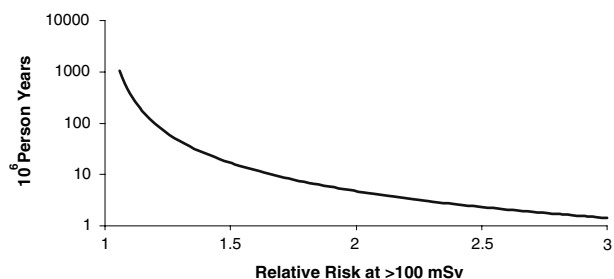
#### Power analysis

Preliminary power analyses, based on dose and confounder (age, sex) distributions characteristic of US nuclear weapons facilities, show that approximately 11 million PY would be required to detect an RR of 1.63 for CLL comparing >100 mSv to a referent category of 0–10 mSv (Fig. 2), with 80% power ( $\alpha = 0.05$ ). Such an RR is expected for non-CLL leukemia following radiation exposure greater than 100 mSv, per the BEIR V model. However, CLL risks associated with radiation may be smaller those associated with other leukemia subtypes [113]. Assuming risks similar to lymphoma (RR = 1.02 at >100 mSv, NCI–CDC working group tables [22]), more than half a billion person years would be needed to detect an association with the specifications listed above.

In order to determine when an updated pooled analysis of occupational cohorts would potentially be informative

**Table 3** Nuclear weapons test participants

Reference	Study population	Analysis	CLL risk estimates
Muirhead et al. [111, 112]	221,357 participants in British tests in Australia & Pacific 1952–1967, followed through 1998	Participants versus non-participants Full follow-up period 2–25 years since participation	RR = 1.16 (90% CI 0.63, 2.13), #CLL in participants = 18 RR = 1.90 (90% CI 0.55, 6.93)
Thaul et al. [37]	68,168 US participants 1951–1957, followed through 1996	SMR Participants versus non-participants	SMR = 0.59, # CLL in participants = 29 Hazard ratio = 1.22 (95% CI 0.71, 2.11)



**Fig. 2** Relative risk versus sample size

for CLL, given the above power calculations, a PY extrapolation analysis (Table 4) was performed for selected cohorts). A pooled cohort mortality study of the US, UK, and Canadian cohorts, with vital status follow-up until 2002, would yield approximately 13.4 million PY (unlagged estimate) and detect with 80% power a minimum RR at >100 mSv of 1.56 and 1.52, where alpha (significance level) is 5% and 10%, respectively (Table 5). Extending follow-up would increase the cumulative PY count for these cohorts, and allow detection of lower relative risks at the same alphas.

However, if a lag period of 15 years is assumed, the PYs decrease greatly, since the first 15 years of follow-up for each worker are ignored. In order to assess the effect of lag on the calculations, the PY extrapolations for the INL and LCCS cohorts (data were readily available) were lagged by 15 years. For these cohorts combined, the PY estimate for 2002 decreased by 42%, while the estimates for follow-up through 2007 and 2012 decreased by 39% and 38%, respectively. Projecting similar PY losses to the combined US, UK, and Canadian cohorts if a 15-year lag is imposed give the following PY estimates: approximately 7.8 million by 2002, 9.2 million by 2007, and 10.5 million by 2012. Thus, with such a lag assumption, which is likely more reasonable than a zero lag, the estimated 11 million PYs required to detect risks similar to radiation-induced non-CLL leukemia (RR = 1.63 at >100 mSv) would not be reached until after 2012.

The Chernobyl cohort could potentially be added to this pool, although there is some dispute over the validity of diagnoses [100, 114]. Using an unlagged PY extrapolation, the Russian Federation Chernobyl workers would be expected to accumulate two million PY by 2002. From 2003–2007 and 2008–2012, another 591,183 and 530,658 PY would be expected, respectively. However, with a 15-year lag, this cohort would not even begin to accrue PY until 2002. The Ukraine and Belarus Chernobyl cohorts combined are of similar size and would be expected to contribute PY of the same order of magnitude as the Russian cohort. Study results are pending on a group of over 100,000 Ukrainian cleanup workers followed in an

NCI International collaborative study, which includes a case-control study of 110 leukemias (number of CLL cases not given). Mean and median doses of 170,000 workers 1986–1989 are 126 and 112 mGy. Belarus supplied 91,000 cleanup workers 1986–1989. Doses are known for only 9% of workers in this group; from this limited data, doses appear to be relatively low, with mean and median doses for the entire time period of 46 and 25 mGy. Mean and median doses for 1986 were 60 and 53 mGy.

## Discussion

### Summary of findings

Evaluation of CLL radiogenicity is hampered by the exclusion of CLL from many analyses, as well as the failure to report CLL-specific results. The majority of occupational and medical radiation epidemiology studies do not examine CLL as an endpoint. While some exclude CLL because of legitimate concerns about ascertainment, others exclude CLL because the authors believe, based on evidence from other studies, that the disease is non-radiogenic. This a priori exclusion of CLL precludes comprehensive assessment of its relation with radiation exposure.

In cohort studies of patients treated with external beam radiation or brachytherapy, risk estimates appear to rise with average time since treatment. However, average follow-up time is strongly related to indication for treatment (malignancy versus benign condition, and type of malignancy). Dosimetry is lacking for most of these studies, but average dose to bone marrow differs by indication for treatment as well. Thus, while it appears that studies with adequate latency tend to show increased risk of CLL after radiation exposure, the small number of studies reporting results, as well as the lack of dosimetry data, limit the interpretation of this suggestive finding. Case-control studies reporting CLL results for medical populations are very limited.

Interestingly, with the exception of a cohort of tuberculosis patients (Davis et al. 1989), all the studies with summary risk estimates below 1.00 were of malignant conditions, whereas studies of benign conditions showed elevated CLL risk estimates, although the elevations were not statistically significant. This difference is likely a function of follow-up time, and the relative survivability of malignant versus benign conditions. In addition, patients treated for malignant conditions, with the exception of testicular and cervical cancer, tend to be older than those treated for benign conditions, and are, therefore, more likely to have follow-up attenuated by competing causes of death.

**Table 4** Person-years extrapolation for selected cohorts of workers monitored for external radiation

Source cohort	N	VS end	Mean dose (mSv)	Follow-up through VS end date PY	Deaths	Follow-up extrapolation		
						Through 2002	Through 2007	Through 2012
						Cum PY	Cum PY	Cum PY
US-LCCS <sup>a, b</sup>	94,517	1996	Not given	2,909,871	23,944	3,497,176	3,730,696	3,913,052
		1994		1,522,815	20,723(15 yr lag)	2,102,522(15 year lag)	2,336,927(15 year lag)	2,519,288(15 year lag)
		1990		(15 yr lag)				
US-INL <sup>b</sup>	36,303	1999	12.7	949,222	6,034	1,037,124	1,172,592	1,290,779
				441,583 (15 yr lag)	5,064 (15 yr lag)	511,291(15 year lag)	635,304 (15 year lag)	755,478 (15 year lag)
UK-National Registry of Radiation Workers <sup>c</sup> Muirhead et al.[26]	124,743	1992	30.5	O = 2,063,300 E = 2,230,182 O/E = 0.93	O = 12,765 E = 12,981 O/E = 0.98	3,182,281	3,661,751	4,098,797
Canada-National Dose Registry Ashmore et al. [27]	201,194	1987	5.69	2,861,093	5,426	5,756,244	6,641,988	7,468,767
TOTAL US, UK, Canada	456,757			8,783,486	48,169	13,472,825	15,207,027	16,771,395
Russian Federation-Chernobyl Ivanov et al.[28]	119,416	1995	107 mGy	Not given	Not given	1,954,069	2,545,252	3,075,910
Total all	576,173					15,426,894	17,752.28	19,847,305

<sup>a</sup> Includes LANL, Hanford, SRS, PNS, ORNL<sup>b</sup> Calculated from raw data files<sup>c</sup> Excluded PY prior to 1955 and ages over 85

**Table 5** End of follow-up, person-years required, detectable risk

End of follow-up (unlagged analyses)	Approx. person-years (millions)	RR at 100 mSv $A = 0.05$	RR at 100 mSv $A = 0.10$
2002	13.4	1.56	1.52
2007	15.2	1.54	1.48
2012	16.8	1.50	1.44

Studies of patients exposed to Thorotrast studies present no compelling evidence of CLL radiogenicity from this type of treatment. The results for  $^{131}\text{I}$  treatment are mixed, with crude risk estimates positive for the two studies with >20 years of follow-up and no cases observed in three studies where follow-up was at most 10 years. However, in the studies with positive overall results, differences by indication for treatment and the lack of a clear dose–response suggests the need for more investigation.

Occupational studies tend to have average follow-up of at least 15 years; however, many report mortality, rather than cancer incidence, and the percent deceased among these cohorts is usually less than 25%, limiting study power. Studies of nuclear facility workers do not demonstrate consistent evidence of CLL radiogenicity; studies of two large cohorts, INL [85] and IARC [25], reported non-significant CLL deficits, while a study of a smaller cohort, LANL [94], reported a significant positive trend for CLL, based on very few cases. Studies of radiologists and radiologic technologists tend to show higher CLL risks for those employed in the early years (prior to 1940 or 1950), when doses were presumably higher; however, the absence of actual dosimetry is a limitation of these studies. Non-significant elevations were also seen in some studies of nuclear test participants compared to non-participant veterans. Two large-multinational studies of airline pilots and crew were generally negative; non-significant elevations were found only among workers with >20 years since first employment and in intermediate dose categories. In occupational studies reporting risk for all leukemia and leukemia excluding CLL, the effects of excluding CLL vary, with some risk estimates increasing and others are decreasing. The confidence intervals for the two outcomes are not mutually exclusive, limiting interpretation and highlighting the need for explicit reporting of CLL risk.

Other issues hinder epidemiologic assessment of CLL radiogenicity. Disease misclassification is problematic, as evidenced by the Muirhead et al. study [111] of nuclear test participants, where six diagnostic discrepancies between CLL and NHL were found and the Weiss et al. [57] study of ankylosing spondylitis, in which a death certified as a CLL was noted as an acute myeloid leukemia in the medical records. Historically, CLL has been difficult

to distinguish from other B-cell malignancies, such as NHL, leading to misdiagnoses [115]. Case ascertainment for mortality studies is particularly problematic because death certificates often fail to identify leukemia subtype [115]. CLL is an indolent disease and may not manifest for decades. In the 1970s, only 30–40% of cases were diagnosed asymptotically [18]. With the advent of routine blood counting, 70–80% of CLL patients are diagnosed incidentally [24]. Ascertainment limitations are more severe for earlier deaths, where histology was not often performed and patients may have been first diagnosed when in blast crisis and, therefore, noted as acute or unspecified leukemia. These misdiagnoses may lead to underascertainment of CLL in the early years of study cohorts. Furthermore, mortality studies likely miss CLL cases, particularly where follow-up is short and only underlying cause of death, as recorded on the death certificate, is considered.

The risk status of study subjects can also complicate interpretation and generalization of study results. Prior exposures or genetic susceptibility contributing to an original malignancy may increase the risk of second primaries, potentially including CLL. Compromises in the immune system, whether genetic, resulting from the original malignancy, or resulting from treatment, may increase this risk. Some “benign” conditions may mark increased susceptibility or an underlying malignancy. For example, in a minority of cases, uterine bleeding could be symptomatic of an undiagnosed uterine cancer. Ankylosing spondylitis has an immune system component and may confer differential susceptibility to malignancies, including CLL. However, in general, patients treated for benign conditions are less likely to have such risk factors than patients treated for malignancies.

Uncontrolled confounding, which may lead to biased results, is particularly problematic in medical studies that fail to differentiate between treatment arms. Occupational studies may also suffer from uncontrolled confounding, as nuclear facility workers were exposed not only to external and internal radiation, but also to a number of potentially carcinogenic chemicals, during employment. Controlling for exposures which increase CLL risk is problematic, as these are generally unknown.

The use of short-lag periods is particularly problematic. Richardson et al. [113] recently published a narrative review on the radiogenicity of CLL emphasizing the importance of adequate follow-up time in studies of CLL; studies having a short follow-up time could potentially miss an effect from ionizing radiation if not enough time has elapsed after exposure for CLL to manifest. The authors suggest that latency for CLL may be upwards by 15 years [113]. Results from the medical cohort studies described in this review support this hypothesis. The

majority of occupational and medical studies employ a two-year lag in analyses of leukemia; though perhaps suitable in the study of acute leukemia, such a lag assumption is probably not consistent with the disease course of CLL.

#### Future directions

Currently, therapeutic radiation is rarely used as treatment for non-malignant conditions; thus new patient populations of this type are unlikely to emerge. Updates of existing patient populations may provide more data on CLL risk, but follow-up of these cohorts generally already exceeds 20 years. In many studies of second malignancies, average follow-up time is quite short, especially for those first primaries which tend to be rapidly fatal. Studies of second primaries in patients with first primaries such as lung cancer, with a five-year survival rate below 20%, are particularly inappropriate for estimating the treatment-induced risk of subsequent CLL. Studies of breast cancer and prostate cancer are somewhat better, although the average age at diagnosis, particularly with prostate cancer, limits long-term survival rates. Testicular cancer may be the most suitable candidate for further study once sufficient follow-up accrues; patients are often young and 15-year survival rates exceed 75%. In the future, progress in diagnosis and treatment may improve patient survival, and hence follow-up time, making these populations more informative for CLL risk. However, the growing use of adjuvant chemotherapy as treatment for many conditions, as well as questions of underlying susceptibility, are problematic for evaluating radiation-associated risk of CLL.

Occupational studies are a more likely source of further information on CLL radiogenicity in the near future. The NIOSH-commissioned CLL-specific results of the IARC 15 country study, with 65 cases of CLL (both underlying and contributing causes) should prove informative, especially in the examination of alternate lag assumptions. Adequate power to detect a CLL risk on the order of radiation-induced leukemia requires a large sample size. Power analyses found that an updated pooled analysis of a number of existing occupational cohorts might garner sufficient person years, depending on the level of excess risk. However, occupational epidemiological studies are unlikely to rule out an association between CLL and radiation if the excess risk is very small (i.e., an RR of 1.02 at >100 mSv per the lymphoma risk model).

The power analysis was performed under several assumptions; deviations from those assumptions would alter the sample size calculations. If the baseline case rate is higher (for instance if both underlying and contributing causes of death were considered in a pooled cohort study,

or if incident CLL cases were included), then the power of the study would increase and fewer PYs would be required. Inclusion of more high-dose workers, such as the Chernobyl group, would increase power to detect an association, although the shorter average follow-up and relatively young age of most Chernobyl workers could have the opposite effect. Conversely, inclusion of many workers with lower doses than those of US cohorts (e.g., Canadian National Dose Registry, mean dose = 5.8 mSv) could decrease power.

With further follow-up, more workers will shift into the older age categories, thereby increasing power. If the actual sex distribution by dose level in the potential pooled study differed greatly from that assumed in the power calculations, power would also be affected, as CLL is twice as prevalent in males as females. The Canadian National Dose Registry population [27] is approximately 50% female; however, the percent female per dose category used in the power calculations ranged from 20% to 35%.

Finally, consideration of incident CLL cases could increase statistical power while avoiding some of the ascertainment issues of death-certificate based studies. Indeed, the differences in results between Canadian incidence and mortality study data suggest a need for further investigation. However, as US cancer registries provide limited, though improving, coverage of the population, the contribution of this data source may be limited.

#### Other issues

Improved understanding of CLL risk conferred by internal, as well as external, radiation exposure is necessary. As populations exposed to internal emitters are smaller and the nature of the exposures diverse, achieving adequate study power while controlling for exposure a variates will be quite difficult. Two occupational populations in the former Soviet Union (Mayak and the Siberian Chemical Industrial Complex at Seversk) may present opportunities for further research on CLL risk following exposure to internal emitters, particularly plutonium. A database including 80,000 bioassays for 8,694 Mayak workers [116] has been developed. A registry of Seversk workers has been created, as well, although most of the plutonium-exposed workers had body burdens below the limit of detection [117]. However, these groups are small and have been already followed at length.

Studies of internally exposed worker populations in the US DOE and the UK may contribute additional information with further follow-up, but these cohorts are often small. Studies to date providing pertinent risk estimates for these workers [94, 118, 119] had 3 CLL deaths at most and are thus of limited value. A case-control study of a specific



internal exposure nested within a pooled population of these workers is likely the most efficient approach to this issue.

Future research into the basic mechanisms of CLL is critical for improvements in epidemiologic evaluation of this disease. Determination of the proper organ for assessing radiation dose and understanding the mechanisms of CLL disease induction (particularly investigation of whether radiation potentially acts as an initiator, a promoter, or a complete carcinogen) will assist with determination of the optimal lag periods for future studies.

## Summary

Up to date there is no conclusive evidence regarding CLL radiogenicity. Occupational studies show inconsistent results for CLL radiogenicity, with some studies reporting decreased CLL risk and others reporting elevations; most results are not statistically significant. The observation of positive point estimates in studies with follow-up times greater than 15 years in the medical studies, and no positive estimates in studies with shorter follow-up, while based on a sample of convenience (availability of follow-up information and CLL results), is suggestive. Specifically, this finding is consistent with a long latency for CLL and highlights the need for studies with adequate follow-up time.

A pooled occupational cohort mortality study of US, UK, and Canadian cohorts with follow-up through 2012 would have approximately 10.5 million person-years (with a 15-year lag). Such a study might be informative for CLL if the risk of this disease is similar to that for other leukemias, but not if the risk more closely resembles that of NHL.

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