

# Reconsideration of chronic lymphocytic leukemia for purposes of compensation.

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I will begin with a summary of my evaluation regarding the association between radiation and chronic lymphocytic leukemia (CLL), then expand upon the rationale behind my opinion, and conclude with comments on the 4 Arguments for including CLL made by EEOICPA stakeholders.

## Summary.

The body of scientific evidence indicates that chronic lymphocytic leukemia (CLL) is not caused by exposure to ionizing radiation at any level of dose. Not one of the major epidemiologic studies of patients exposed to medical radiation or workers exposed to occupational radiation has reported a statistically significant increase in CLL. Authoritative committees on radiation effects and cancer such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the International Agency for Research on Cancer (IARC) have concluded that CLL is not caused by ionizing radiation. CLL appears etiologically and clinically a lymphoma and differs from the other forms of leukemia. Lymphomas also have not been convincingly linked to ionizing radiation. In the same epidemiologic studies that find significant increases in myeloid leukemia, no increases in CLL are found despite CLL being the most frequent leukemia among adult Western populations. The etiologic factors that cause CLL are not well defined but are different from those factors that cause other forms of leukemia. For example, benzene causes myeloid leukemia, but apparently not CLL. Cigarette smoking causes myeloid leukemia, but not CLL. Alkylating agents cause myeloid leukemia, but not CLL. Thus based on epidemiologic studies of radiation finding no evidence for an association with CLL, coupled with the etiologic and clinical differences between CLL and the other forms of leukemia that are caused by radiation, CLL should not be considered a radiation-inducible cancer.

## Authoritative Radiation Committees.

Below I reference the conclusions reached by two scientific committees that have addressed the association between radiation and CLL. The first is the International Agency for Research on Cancer: IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Volume 75. Ionizing Radiation, Part I: X- and gamma ( $\gamma$ )-radiation and neutrons. Lyon, France. IARC, 2000.

“Tissues that are apparently less susceptible or in which cancers are induced only at relatively high-doses include the brain, bone, uterus, skin and rectum. *Some cancers have not been linked convincingly to exposure to radiation; these include chronic lymphocytic leukemia, Hodgkin disease, multiple myeloma, non-Hodgkin lymphoma, and cancers of the cervix, testes, prostate, pancreas and male breast*” (page 233, italics added).

A subsequent review is found in International Agency for Research on Cancer: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 78. Ionizing Radiation, Part 2: Some Internally Deposited Radionuclides. Lyon, France. IARC, 2001.

“Various types of leukaemia, with the exception of chronic lymphocytic leukaemia and adult T-cell leukaemia, are known to be caused by external irradiation, as shown among the atomic bomb survivors” (Page 70).

“Similarly, the incidence of and mortality from non-chronic lymphoid leukaemia and myelodysplastic syndrome is increased 5-20-fold in Thorotrast-treated individuals, whereas the risk for chronic lymphoid leukaemia was not increased in any study” (page 186).

“There is sufficient evidence in humans that diagnostic injection of thorium-232 as stabilized thorium-232 dioxide in colloidal form (Thorotrast) causes primary liver cancer, including haemangiosarcomas, and leukaemia, excluding chronic lymphocytic leukaemia.” (page 478)

The second committee is the United Nations Scientific Committee on the Effects of Atomic Radiation(UNSCEAR 2000).

“In the review in the UNSCEAR 1994 Report, it was concluded that the incidence of acute leukaemias or of chronic myelogenous leukaemia exhibits strong associations with exposure to external low-LET radiation. In contrast, several large studies of groups with medical exposures (e.g. [Boice 1987; Curtis 1992, 1994; Weiss 1995]) show no association between radiation and CLL. Although the Life Span Study of atomic bomb survivors also fails to show an association with CLL, the medical studies provide much stronger evidence, owing to the low baseline rates in Japan”. (Pages 346-7)

“... observations from studies of cancer incidence among the survivors of the atomic bombings, namely that radiation-induced skin cancers are limited primarily to basal-cell carcinomas [Ron 1998a; Thompson 1994] and that chronic lymphatic leukaemia and virus-related adult T-cell leukaemia [Preston 1994] do not appear to be radiation-inducible, may have significant implications for biomedical research as well as radiological protection”. (Page 308)

**Conclusion.** The scientific committees that periodically examine the risk of cancer following radiation exposure continue to conclude that CLL is not induced by radiation. They rely not only on the studies of Japanese atomic bomb survivors, but also on the numerous large-scale studies of patients and workers that also fail to find an association between radiation and CLL.

## Individual Scientists.

This section presents statements made by radiation epidemiologists and leukemia specialists on the association between CLL and radiation.

Robert Miller and Gilbert Beebe (National Cancer Institute). Leukemia, lymphoma and multiple myeloma. In (Upton AC, Albert RE, Burns FJ, Shore RE, Eds). Radiation Carcinogenesis. Elsevier, New York, 1986, pp 245-260.

“CLL has not been induced by radiation in susceptible (occidental) people.” (Page 248)

“An early report of excess lymphoma among A-bomb survivors (Anderson and Ishida, 1964) has not been confirmed by later experience. Study of the death certificates of the survivors for 1950-1978 has indicated no real excess of lymphoma, even among the most heavily exposed (Kato and Schull, 1982). CLL, which is clearly not excessive in A-bomb survivors or in British patients given radiotherapy for ankylosing spondylitis, is etiologically and clinically a lymphoma, and different from other forms of leukemia”. (Page 254)

“Groups at high risk of lymphoma are immunologically deficient, either for genetic reasons (ataxia telangiectasia [AT], X-linked lymphoproliferative syndrome, Wiskott-Aldrich syndrome, or combined immunodeficiency disorders), or because of therapy, as in immunosuppression for renal transplantation. These groups generally have a normal risk of leukemia, a notable exception being AT in which ALL occurs excessively but with a much lower risk than lymphoma (reviewed by Miller, 1977). Groups that are genetically at high risk of leukemia (e.g., those with Down's syndrome or Fanconi's anemia) are not usually at high risk of lymphoma. The pathogenesis of lymphoma is apparently different from that of nonlymphocytic leukemia, as indicated by the dissimilar epidemiologic characteristics of the two groups of neoplasms”. (Page 254)

Maria Sgambati, Susan Devesa, Martha Linet (National Cancer Institute). Chronic lymphocytic leukemia: epidemiologic, familial and genetic aspects. In: Chronic lymphoid leukemia: Scientific Advances and Clinical Developments (Chelson B, Ed ) New York, Marcel Dekker, Inc , 2001 pp 33-62.

“Little or no evidence exists that exposure to ionizing radiation is linked with risk of CLL.”  
(Page 40)

Bruce Cheson (Vincent Lombardi Cancer Research Center). The chronic lymphocytic leukemias. In DeVita VT, Hellman S, Rosenberg SA (Eds). Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Ed. Lippincott Williams and Wilkins, Philadelphia, 2001, p 2447

“CLL is one of the few leukemias that does not appear to be associated with prior exposure to ionizing radiation, chemicals, or drugs.” (Page 2447)

Elaine Ron (Radiation Epidemiology Branch, National Cancer Institute). Ionizing radiation and cancer risk: evidence from epidemiology. Radiat Res 150(5 Suppl):S30-41, 1998.

“Chronic lymphocytic leukemia, Hodgkin's disease, and cancers of the pancreas, prostate, testis and cervix have rarely been related to radiation exposure.” (Page S38)

Mark Little, Helen Weiss, John Boice, Sarah Darby, Nick Day, Colin Muirhead (National Radiological Protection Board, UK; Oxford University; Cambridge University; IEI). Risks of leukemia in Japanese atomic bomb survivors, in women treated for cervical cancer, and in patients treated for ankylosing spondylitis. Radiat Res 152:280-92, 1999.

“Significant dose-related excesses of acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and acute lymphocytic leukemia (ALL) have been observed in the Japanese atomic bomb survivors (Preston 1994). Various combinations of these leukemia subtypes have also been observed in excess in the IRSCC patients (Boice 1987), in the UK ankylosing spondylitis patients (Weiss 1995), and in other irradiated groups (UNSCEAR 1994). In contrast, in the atomic bomb survivors (Preston 1994) and in most of the other major groups of exposed persons (UNSCEAR 1994; Boice 1987; Weiss 1995; Curtis 1994), chronic lymphocytic leukemia (CLL) has not been associated with an increased risk from exposure to radiation.”

Michael Keating (M.D. Anderson Cancer Center). Chronic lymphocytic leukemia. In Henderson ES, Lister TA, Greaves MF (Eds). Leukemia, 7<sup>th</sup> Ed. Saunders, Philadelphia, 2002, pp 656-691.

“The cause of CLL is unknown. Evidence for an association between benzene and CLL is weak despite its known role in the etiology of some cases of acute myelogenous leukemia. ... there has been no association of CLL with exposure to ionizing radiation.” (Page 656).

Charles Singer and Anthony Goldstone (University College London Hospitals NTS Trust). Chronic lymphocytic leukaemia and other chronic lymphoid leukaemias. In Souhami RI, Tannock I, Hohenberger P, Horiot J-C (Eds). Oxford Textbook of Oncology, 2<sup>nd</sup> Ed. Oxford, Oxford University Press, 2002, pp 2255-2282.

“B-cell chronic lymphocytic leukaemia (CLL) is the most common leukaemia among adults in Europe and North America, where it accounts for 30 to 40 per cent of all leukaemia diagnoses. ... CLL has not been linked with occupational exposure to radiation or other environmental sources of high or low-level radiation.” (Pages 2255-6).

John Boice (Vanderbilt University, International Epidemiology Institute). Radiation-induced leukemia. In Henderson ES, Lister TA, Greaves MF (Eds). Leukemia, 7<sup>th</sup> Ed. Saunders, Philadelphia, 2002, pp 152-169.

“... with the exception of ALL, cancers of lymphoid cells have not been convincingly linked to radiation exposure. In particular, CLL has not been found to be associated with irradiation in any major epidemiologic . Studies of the atomic bomb survivors also failed to detect an association between radiation dose and incidence of adult T cell leukemia, a disease in which the human T-lymphotropic virus 1 is thought to play a causal role (see Chapters 10 and 30). Whether radiation causes lymphoma and myeloma remains an unresolved question. In summary, ionizing radiation is a clastogen that deposits energy at random in tissues, and chromosome rearrangements appear to be causally involved in the pathogenesis of cancers of myeloid and lymphoid cells. Yet, susceptibility to radiation-induced cancer appears to vary widely among different subsets of marrow derived cells. This underscores the importance of lineage-specific developmental processes and, perhaps, the heterogeneity of progenitor cell populations for blood cell malignant neoplasms (see Chapter 2). Those cancers most closely associated with exposure to ionizing radiation, namely, CML, AML, and perhaps some types of ALL as well as several preleukemic syndromes, apparently originate in primitive, multipotential stem cells. CLL, lymphoma, and multiple myeloma, on the other hand, are thought to arise from mature, differentiated lymphoid cells. One would nonetheless expect radiation-induced genetic damage in a pluripotent stem cell to be propagated to descendants that differentiate along the lymphoid line. Why this would not be related to increased cancer risk is unclear. Perhaps the balance between cell transformation and inactivation as a function of radiation dose differs between lymphoid cells and those of other lineages. Alternatively, other genetic changes or developmental events, possibly immunologic in nature, might be rate limiting to cancer development in cells committed to this lineage.” (Page 154)

**Conclusion.** Radiation specialists and leukemia experts are in general agreement that radiation is not a cause of CLL.

## **Agents, Including Radiation, That Cause Myeloid Leukemia But Apparently Not CLL.**

This section briefly discusses several of the exposures that cause myeloid leukemia but apparently not CLL.

### **Radiation.**

Radiation causes myeloid leukemia and most other forms of leukemias with the exception of CLL and adult T-cell leukemia. Radiation also has not convincingly been associated with increases in lymphomas, which are clinically and etiologically similar to CLL. Table 1 lists the major epidemiologic studies of radiation exposed populations and the reported associations with leukemia (other than CLL), CLL and non-Hodgkin's lymphoma (NHL). The strength and significance of reported associations come from UNSCEAR (2000), IARC (2000, 2001) and individual studies listed and discussed in Boice (Ionizing Radiation. In: Schottenfeld D, Fraumeni JF Jr (Eds). Cancer Epidemiology and Prevention, 3<sup>rd</sup> Ed. Oxford University Press, New York, in press).

It can be seen in Table 1 that while many populations show an increased risk of leukemia (other than CLL), there are none that report a statistically significant association between radiation and CLL (or NHL).

In Table 2, over 20 major studies of irradiated populations are listed, the number of CLL cases are presented along with the estimates Relative Risk (RR) for radiation. Not one study has reported a significant increase in CLL among exposed populations. Few studies report elevated risks.

## **Benzene**

“Although evidence was considered sufficient to designate benzene as a Group 1 carcinogen for acute myeloid leukemia, little evidence has implicated an association with CLL (Rinsky 1987; Utterback 1995; Hayes 1997).”  
(Sgambati 2001).

“Evidence for an association between benzene and CLL is weak despite its known role in the etiology of some cases of acute myelogenous leukemia.”  
(Keating 2002)

“... chronic lymphatic leukemia, a disease that has not been shown conclusively to be caused by benzene.”  
(Goldstein 2004)

## **Tobacco Smoke**

“The study of the effects of smoking on leukaemia presents a problem, because leukaemia is not one disease with a specific etiology, but a combination of several diseases that have a pathological characteristic in common (namely, an abnormal number of white cells in the blood) and which may have — and in some respects certainly do have — different causes. ... Indeed even the acute and chronic forms have seldom been studied separately (although chronic lymphoid leukaemia is sometimes distinguished and may be classed with lymphomas).” (Page 821, IARC Monograph 83, 2004).

“There is sufficient evidence in humans that tobacco smoking causes cancer of the lung, ... and bone marrow (myeloid leukaemia).” (Page 1187)

“The data for lymphoid leukaemia are very different. Only two of eight studies provide any evidence of an increased risk associated with smoking and neither case was the excess risk statistically significant.” (Page 822).

“For the most part, case-control studies and cohort studies show a difference in risk between myeloid and lymphoid leukaemias.” (Page 823).

## **Drugs and alkylating agents**

“CLL is one of the few leukemias that does not appear to be associated with prior exposure to ionizing radiation, chemicals, or drugs.” (Cheson BD. The chronic lymphocytic leukemias. In DeVita VT, Hellman S, Rosenberg SA (Eds). Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Ed. Lippincott Williams and Wilkins, Philadelphia, 2001, p 2447)

“To date, only chronic lymphocytic leukemia has not been convincingly associated with prior exposure to chemotherapy.” (Van Leeuwen FE, Travis LB. Second cancers. In DeVita VT, Hellman S, Rosenberg SA (Eds). Cancer. Principles and Practice of Oncology, 6<sup>th</sup> Ed. Lippincott Williams and Wilkins, Philadelphia, 2001, p 2942)

**Conclusion.** Radiation is not the only agent that can cause myeloid leukemia but apparently not CLL. Benzene, tobacco, and alkylating agents (e.g., cyclophosphamide) are all associated with excess occurrence of myeloid leukemia but not CLL. All of these agents are clastogens (break chromosomes) suggesting, among other possibilities, that the mechanisms involved in the induction of CLL, an immunological deficiency, may differ from those that cause myeloid leukemia.

## ARGUMENTS FOR INCLUDING CLL.

EEOICPA stakeholders have advanced the following arguments for including CLL:

(1) Of the hundreds of different types and sub-types of cancer, including many with sparse evidence of radiogenicity, only CLL is specifically excluded from compensation under EEOICPA. It is simply not plausible that CLL could be the only type of cancer that can not possibly be induced by some level of radiation. Moreover, there is no scientific evidence that convincingly demonstrates it is non-radiogenic.

*NIOSH comment: NIOSH does not assert that evidence proves CLL is non-radiogenic, only that the weight of the evidence has not supported the case for radiogenicity.*

**Boice comment.** The stakeholders are correct in stating that “it is not plausible that CLL could be the only type of cancer that can not possibly be induced by some level of radiation”. There are other cancers that have not been convincingly linked to ionizing radiation as discussed in UNSCEAR 2000, IARC 2000 and 2001 and in many general reviews. These other cancers include Hodgkin’s disease, non-Hodgkin’s lymphoma, multiple myeloma, malignant melanoma, cervical cancer, pancreatic cancer, testicular cancer, kidney cancer, among others. Further, some cancers are induced by radiation only at large, therapeutic doses, such as bone cancer, connective tissue cancer, skin cancer, uterine cancer and rectal cancer. The original NIH tables in 1985 did not consider that all cancers were potentially inducible by radiation but relied upon the scientific evidence at that time to select those for which significant risks and consistent elevations were observed in exposed populations. Since there are now 100s of studies of exposed populations, one may find, by chance, the elevation of a particular cancer in one or a few investigations. However, it is the consistency of studies that is important. That is, do the well-designed studies with good radiation dosimetry find consistent evidence for dose-response relationships or elevations in cancer risk? The answer is yes for myeloid leukemia (Table 2). The answer is no for CLL and NHL and several other cancers (Table 2). While epidemiology is not capable of proving the negative nor is it capable of detecting very low risks, epidemiology can provide the background from which reasonable judgments can be made. The weight of evidence supports a conclusion that CLL is not induced by radiation.

(2) A major reason for excluding CLL was the apparent absence of excess risk among the Japanese A-bomb survivor cohort. However, the reported incidence of CLL varies widely among populations throughout the world. In fact, CLL is rare among the Japanese population and extremely rare among Japanese females (the majority of the A-bomb cohort) prior to age 70. Thus, the ability to detect excess CLL risk due to radiation exposure from atomic bombs is poor.

*NOSH comment: NOSH agrees that the statistical power to detect excess CLL risk among the Japanese survivor cohort is limited.*

**Boice comment.** Most of the evidence that radiation does not cause CLL comes from the much larger and powerful studies of patients treated with radiation (UNSCEAR 2000; Little 1999), and not from the study of Japanese A-bomb survivors. It is true that the background rates for CLL are much lower in Japan than in western countries (there were only 6 deaths due to CLL in the A-bomb study (Preston et al 2004)), and this low rate limits the statistical power to detect an increased risk. It is interesting to note, however, that CLL is the most common leukemia occurring in Western adults and yet no major study has found a significant association between radiation and CLL, while finding associations for the less frequent types of leukemia.

(3) Hairy cell leukemia (HCL) is a slowly progressing lymphocytic leukemia. Because its symptoms are similar to CLL, it has sometimes been misdiagnosed as CLL. In fact, the Hairy Cell Leukemia Research Foundation refers to it on their Web site as a type of CLL. Misdiagnoses of cancers of the blood and bone marrow were much more common in the time period during which many EEOICPA claimants were diagnosed with cancer, i.e., before improvements in diagnostic techniques had been achieved. For that

reason, it's very likely that medical records for some claimants may contain inaccurate diagnoses. Despite the similarities between HCL and CLL and the diagnostic problems associated with those similarities, HCL is eligible for compensation under EEOICPA, but CLL is not. The disparity in treatment of these diseases is neither fair nor justified.

*NOSH comment: NOSH defers to NCI for expertise on the classification of cancers, and NCI regards HCL and CLL as separate diseases. Moreover, HCL was covered under the original NIH Radio-Epidemiological Tables, whereas CLL was excluded. Diagnostic issues notwithstanding, NCI has consistently maintained the distinction between CLL and HCL in its updates to those tables. On the other hand, it should also be noted that this distinction is not universal; for example, the United Kingdom's radiation compensation program excludes CLL and HCL from compensation eligibility.*

**Boice comment.** Similar to CLL, there are no studies that have convincingly linked HCL to ionizing radiation. However, there are few studies that have evaluated HCL. There were only 2 cases of HCL among atomic bomb survivors (Preston 1994).

(4) NIOSH convened a public meeting in Washington, DC on July 21, 2004 to seek input on gaps in CLL research. This meeting featured a panel discussion of experts from the fields of epidemiology, medicine, radiobiology, and related health sciences. There was a clear consensus among this NIOSH-convened panel that scientific evidence is inconclusive with respect to CLL's association with ionizing radiation. The intent of EEOICPA, and the often stated intention of NIOSH in carrying out its mandate under EEOICPA, is to err on the side of the claimant whenever scientific evidence is lacking. The arbitrary exclusion of CLL, without regard to an individual's degree of radiation exposure or to the stochastic nature of cancer risk, is clearly contrary to that intent.

*NIOSH comment: The public meeting referred to above was convened by NIOSH's Health-Related Energy Research Branch (HERB) as part of an ongoing effort to investigate the possible relationship between ionizing radiation and CLL. HERB has not yet released a written summary report of that meeting. However, OCAS staff who attended had the impression that, although expert opinion was rather wide-ranging, at least some panel members seemed to agree that scientific evidence is inconclusive with respect to CLL's etiology and to its association with radiation. Pending release of the HERB report, NIOSH reaffirms its commitment to err on the side of the claimant when the state of scientific knowledge is lacking.*

**Boice comment.** The absence of evidence for an association between radiation and CLL does not mean that there is an absence of data. There are numerous studies of irradiated populations, other than of the atomic bomb survivors, that find evidence for increased risks of myeloid leukemia by no evidence for increased risks of CLL. Excluding CLL is not arbitrary but rather is consistent with the conclusions reached by all authoritative national and international committees, i.e., that CLL is not induced by radiation. As discussed above, there are several agents other than radiation that increase the risk of myeloid leukemia but not CLL, e.g., benzene, tobacco and alkylating agents. It is not surprising that ionizing radiation would not increase the risk of CLL.

But there is a general issue being raised regarding the distinction between political decisions and scientific evidence. There are a number of cancers other than CLL that have not been associated convincingly with exposure to ionizing radiation. Based on the weight of scientific evidence (and consistent with the NIH Radiological Tables 1985; UNSCEAR 2000; IARC 2000, 2001) there would be little justification for including them in a compensation scheme. Yet they were included based on a political directive to err on the side of compassion. This political decision satisfies the wishes of society through the political process. However, it should be recognized that there is little scientific justification for including cancer sites that have not been consistently or convincingly linked to ionizing radiation. Epidemiologic studies of exposed populations have been conducted over the past 100 years so there is not a dearth of knowledge from which sound scientific judgments can be made. CLL is one of several cancers for which the body of scientific knowledge is rather convincing that radiation is not a contributing cause.

## RECENT ARTICLE BY RICHARDSON ET AL 2005

After preparing my opinion, an article by Richardson et al (2005) was published providing arguments why CLL should be included in the compensation scheme. While stating that “the epidemiologic evidence of association between external exposure to ionizing radiation and CLL is weak”, the authors go on to conclude that “epidemiologic findings are consistent with a hypothesis of elevated CLL mortality risk after a latency and morbidity period that spans several decades” and “Our findings in this review suggest that there is not a persuasive basis for the conclusion that CLL is a nonradiogenic form of cancer.” (Abstract). I believe the arguments presented are tenuous for the following reasons.

- (1) Many studies of irradiated populations find elevated risks of myeloid leukemia but not one major study (Table 2) reports a statistically significant elevation of CLL, even for persons followed for several decades. There is thus no epidemiologic evidence that CLL is a radiogenic form of cancer.
- (2) CLL is the most common adult leukemia in western populations. Many studies have follow-up periods exceeding 30 years and yet no significant elevation in CLL *incidence* or mortality has been reported. The latency period for most solid cancers also spans several decades and this has not precluded the detection of significant associations with radiation.
- (3) The absence of an association between radiation and CLL is consistent with studies of other clastogens (agents that break chromosomes) such as benzene, cigarette smoke and alkylating agents that also do not find convincing evidence for increased risk of CLL. Thus the mechanistic arguments associated with chromosome damage are not strongly supported.
- (4) CLL is clinically and etiologically a lymphoma, and lymphomas also have not consistently or convincingly been associated with ionizing radiation exposure.
- (5) Specific studies that Richardson et al (2005) relied upon and highlighted in their Table as “evidence for radiation risk” are discussed below.

Ankylosing spondylitis (Weiss 1995). Only 7 CLL deaths were observed and 4.9 were expected. However, Weiss et al. noted that one of the CLL deaths had been misclassified and that the correct cause of death was AML based on medical record review. Although CLL was elevated for the time period 25+ years after radiotherapy, for the time interval 15-24 years after radiotherapy, the RR was 0.0 indicating a deficit of CLL. The p-value for an increasing risk with time was not significant ( $p=0.78$ ). Albeit based on only 1 case, the RR among non-exposed patients was 2.0 and higher than the exposed patients. General population studies of arthritics (not exposed to radiation) find elevated risks of CLL of the order of 1.43. The ankylosing spondylitis series provides little to no support for CLL being a radiogenic cancer.

Benign disorders of the locomotor system (Damber 1995). No findings in this study were statistically significant. In fact, the risks for myeloid and acute leukemias, frequently found to be elevated following radiotherapy, were not significantly increased. For all irradiated patients, including the patients exposed to  $<0.2$  Gy (200 mSv), the RR was 1.07. There were 19 CLL cases in this “low dose” group and not “1” as reported in the review. There was no evidence of a dose response, i.e., the RR for the 0.2-0.5 Gy and  $>0.5$  Gy intervals were 1.17 and 1.18 based on 15 and 16 CLL cases, respectively. This study provides little to no support for CLL being a radiogenic cancer.

Benign gynecologic disorders (Inskip 1993). The dose-response relationship for CLL was negative and there were no CLL cases among women with doses  $> 0.20$  Gy. The risk of CLL among exposed women was 1.8 but it was also elevated among non-exposed patients (RR 1.6). The authors concluded “there was no evidence of effects attributable to radiotherapy for chronic lymphocytic leukemia [relative risk (RR) = 1.1].” This study is consistent with the comparable



study of women irradiated for similar conditions in Scotland (Darby 1994) finding no evidence to support CLL to be a radiogenic form of cancer.

Breast cancer (Curtis 1989). A nonsignificant increase in CLL was reported based on 4 exposed cases of CLL, however, the population expected number of breast cancers in this cohort was 2.2 (Harvey 1985). There also was no association between radiotherapy and the other forms of leukemia (RR=1.0, n=33). Other studies of breast cancer patients fail to find an association between radiotherapy and CLL (Boivin 1986; Ewertz 1985). A large-scale population-based study in Denmark of 54,964 women, of whom 69 percent received radiotherapy, showed no increase in CLL (RR=1.0, n=29). There is thus no significant or consistent evidence that radiotherapy for breast cancer increases the risk of CLL.

Again it is worth repeating that no major epidemiologic study (Table 2) finds a significant risk of CLL following radiation, including the atomic bomb survivors, patients treated for cancer, patients treated for non-malignant conditions with radiotherapy, patients who received large numbers of x-ray fluoroscopic examinations, radiologists, x-ray technologists, and others. In contrast, many of these studies have reported increased risks of solid cancers several decades after exposure as well as significant increases in the risk of myeloid and other forms of leukemia (excluding CLL).

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**Table 1. Epidemiologic studies of populations exposed to ionizing radiation and subsequent risk of leukemia other than CLL, CLL and nonHodgink lymphoma (NHL) by type of exposure and strength and significance of the radiation association.**

Type of exposure	Study	Leukemia (other than CLL)	CLL	NHL
Atomic bomb	Japanese survivors	+++ <sup>1</sup>	••	±
	Weapons test participants	±	••	••
Radiotherapy	Cervical cancer	++	••	±
	Endometrial cancer	+	••	••
	Breast cancer	±	••	••
	Ankylosing spondylitis	+++	••	±
	Menstrual disorders	++	••	••
	Scalp ringworm	+	••	••
Diagnostic X-rays	X-ray fluoroscopy (tuberculosis)	••	••	••
	General patient exposures	±	••	••
Radionuclides	Hyperthyroidism (I-131)	••	••	••
	Thorotrast	++	±	±
	Radium	••	••	••
Occupation	Radiologists, U.S.	++	••	±
	X-ray workers, China	++	••	••
	Radiologists, U.K.	±	±	±
	Nuclear energy workers	±	••	••

<sup>1</sup> +++ denotes highly significant finding; ++ meaningful association; + suggested but unconfirmed; ± equivocal; ••no evidence for a significant increase in risk.

**Table 2. Major epidemiologic studies of exposed populations reporting information on the risk of CLL. Number of CLL cases are presented along with the relative risk (RR) associated with radiation exposure.**

Population (reference)	No. CLL <sup>1</sup>	RR	Comment
Japanese Bomb Survivors (Preston 1994; 2004)	6	NR <sup>2</sup>	More than 50% of myeloid leukemia cases were attributed to radiation. CLL was not increased. CLL is rare in Asian populations.
International Cervical Cancer Study – Cohort (Boice 1985)	18	0.81	Myeloid leukemia was significantly increased in cohort study. CLL is the most common leukemia in Western adults.
International Cervical Cancer Study – Case-Control (Boice 1987)	52	1.03	Nested case-control study found no radiation association with CLL. Significant two-fold risk for myeloid leukemia observed.
Radiotherapy for Cervical Cancer (Kleinerman 1995)	25	0.77	CLL risk higher (RR=1.2, n=8) among non-exposed. A significant risk of non-CLL was reported.
Radiotherapy for Uterine Corpus Cancer (Curtis 1994)	54	0.90	Significant 1.92 RR found for the other leukemias.
Radiotherapy for Breast Cancer (Curtis 1989)	10	1.84	90% CI (0.5-6.7). Elevation not statistically significant and based on 4 exposed cases.
Radiotherapy for Breast Cancer (Boivin 1986)	12	1.00	Based on 2 exposed cases.
Radiotherapy for Spondylitics (Weiss 1995)	7	1.44	Non-significant increase 95% CI (0.6-2.8). For one death certified as CLL, the medical notes indicated AML. Comparable increase (RR 2.0) seen among non-exposed. CLL has been reported increased (RR 1.43) in some non-irradiated arthritic populations (Gridley 1993).
Radiotherapy for Arthritic Conditions (Damber 1995)	50	1.07	Mean dose to bone marrow 0.39 Gy, no evidence of dose-response.
Radiotherapy for Benign Gynecologic Disease (Inskip 1993)	21	1.13	Negative dose-response.

Radiotherapy for Metropathia Haemorrhagica (Darby 1994)	1	NR	2,067 women treated. "Thus, as in other irradiated populations, there is no evidence of an excess of chronic lymphocytic leukaemia in these women." (Page 799).
Radiotherapy for Tinea Capitis (Ron 1988)	0	0.00	Significant risk (RR 2.3) of myeloid leukemia observed among 10,834 irradiated children. Age at follow-up young.
Multiple Chest Fluoroscopy During TB Treatments (Davis 1989)	3	0.00	No CLL occurred among 6,285 patients who received on average 77 chest x-ray fluoroscopies. 3 cases occurred among the non-exposed.
Diagnostic X-rays (Boice 1991)	207	0.66	No evidence for dose-response over diagnostic x-ray score.
I-131 Radiotherapy for Hyperthyroidism (Ron 1998a)	24	0.83	Negative dose-response. RR (0.83) presented for highest dose category.
International Worker Study (Cardis 1995)	27	0.91	RR estimated at 100 mSv. No evidence for a dose-response.
UK Worker Registry Study (Muirhead 1999)	18	0.81	No evidence for a dose-response.
Hanford, Oak Ridge, Rocky Flats (Gilbert 1993)	15	NR	Negative dose-response.
UK Weapons Test Participants (Muirhead 2003)	15	0.54	Suggested increase in other forms of leukemia, but not CLL.
USA Weapons Test Participants (Thaul 2000)	29	0.69	SMR based on 68,168 test participants.
USA Radiologists (Lewis 1963)	0	NR	RR of 3.0 for leukemia (n=12) but no CLL deaths reported.
U.K. Radiologists (Smith 1981; Berrington 2001)	3	3.3	Non-significant increase 95%CI (0.7-9.7). Authors state "the excess is not quite statistically significant and it may be a chance finding". Non-significant and lower risk for non-CLL (RR 2.1, n=5). Computation of expected values uncertain and could be underestimated.
Chinese X-ray Workers (Wang 2002)	1	<1.00	Significant risk of non-CLL reported (n=44). CLL rare among Chinese.

<sup>1</sup> Generally includes all cases reported in each study including those with no or low dose exposures.

<sup>2</sup> NR denotes not reported.