Ionizing Radiation and Chronic Lymphocytic Leukemia

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The U.S. government recently implemented rules for awarding compensation to individuals with cancer who were exposed to ionizing radiation while working in the nuclear weapons complex. Under these rules, chronic lymphocytic leukemia (CLL) is considered to be a nonradiogenic form of cancer. In other words, workers who develop CLL automatically have their compensation claim rejected because the compensation rules hold that the risk of radiation-induced CLL is zero. In this article we review molecular, clinical, and epidemiologic evidence regarding the radiogenicity of CLL. We note that current understanding of radiation-induced tumorigenesis and the etiology of lymphatic neoplasia provides a strong mechanistic basis for expecting that ionizing radiation exposure increases CLL risk. The clinical characteristics of CLL, including prolonged latency and morbidity periods and a low case fatality rate, make it relatively difficult to evaluate associations between ionizing radiation and CLL risk via epidemiologic methods. The epidemiologic evidence of association between external exposure to ionizing radiation and CLL is weak. However, epidemiologic findings are consistent with a hypothesis of elevated CLL mortality risk after a latency and morbidity period that spans several decades. Our findings in this review suggest that there is not a persuasive basis for the conclusion that CLL is a nonradiogenic form of cancer. *Key words:* **chronic lymphocytic leukemia, compensation, ionizing radiation, radiogenicity.** *Environ Health Perspect* **113:1–5 (2005). doi:10.1289/ehp.7433 available via *http://dx.doi.org/* [Online 21 October 2004]**

Less than 5 years after the atomic bombings of Hiroshima and Nagasaki, it was established that there was an excess of leukemia among the atomic bomb survivors (Committee for the Compilation of Materials 1981). Japanese physicians noted the unusual number of leukemia cases among survivors, and researchers associated with the Atomic Bomb Casualty Commission (ABCC) subsequently confirmed the observation in a series of epidemiologic surveys (Folley et al. 1952; Valentine 1951). When examined by leukemia subtype, researchers with the ABCC reported substantial excesses of acute forms of leukemia and chronic myeloid leukemia among A-bomb survivors. In contrast, no excess of chronic lymphocytic leukemia (CLL) was observed (Finch et al. 1969; Ishimaru et al. 1969).

A few years later, Court-Brown and Doll (1957) reported the results of a study of mortality among adult British males who had received X-ray therapy for an arthritic condition (ankylosing spondylitis). When examining leukemia by subtype, it was noted that in the first 5 years postirradiation, deaths due to acute forms of leukemia and chronic myeloid leukemia were in substantial excess among these patients. The researchers found no excess of CLL (Court-Brown and Doll 1965; Darby et al. 1987). These findings, and their consistency with those of the A-bomb survivor studies, led investigators to postulate that there were differences in the radiogenicity of leukemia by subtype, with CLL being much less readily inducible by exposure to ionizing radiation than other types of leukemia (Darby et al. 1987).

Over time, this hypothesis has come to be expressed more strongly (Department of Health and Human Services 2002). Although most lymphatic and hematopoietic tissues are considered to be extremely sensitive to the carcinogenic effects of ionizing radiation, it is routinely presumed that CLL incidence is entirely insensitive to the carcinogenic effects of radiation. This assertion has become institutionalized in the U.S. Energy Employees Occupational Illness Compensation Program, under which all claims for CLL must be rejected because of the presumption that the risk of radiation-induced CLL is zero (Department of Health and Human Services 2002). In this article, we review the basis for the current presumption that CLL incidence is entirely unaffected by ionizing radiation exposure.

Methods

In this article we present a review of the molecular, clinical, and epidemiologic evidence regarding the radiogenicity of CLL. We begin with a review of the current understanding of the molecular basis of CLL. Next, we review the clinical attributes of CLL and discuss the implications for etiologic research. Finally, we consider the epidemiologic literature on associations between external exposure to ionizing radiation and CLL risk. We focus on studies that have played a prominent role in the literature on the induction of leukemia, and specifically CLL, by ionizing radiation [National Research Council, Committee on the Biological Effects of Ionizing Radiation (BEIR V) 1990; United Nations Scientific Committee on the Effects of Atomic Radiation 2000]. Studies of the effects of exposure to ionizing radiation *in utero* or in childhood (e.g., for thymic enlargement or tinea capitis) were not included in this review because the average age of study participants at the end of follow-up tended to be less than the age at which CLL typically occurs.

The Revised European American Lymphoma classification scheme (Harris et al. 1994), which is widely accepted and was adopted by the World Health Organization, considers B-cell CLL and small lymphocytic lymphoma [SLL, a subtype of non-Hodgkin's lymphoma (NHL)] to be a single disease entity, in recognition of the biologic and clinical similarities between these B-lymphocyte malignancies (Harris et al. 1999). Epidemiologic evidence of associations between ionizing radiation and risk of SLL would therefore be of interest in the context of this evaluation. However, epidemiologic studies have only recently begun to evaluate risk factors for SLL, and studies available for this review did not report results specifically for SLL.

Many of the epidemiologic studies that we reviewed reported results of analyses of standardized mortality ratios (SMRs) or standardized incidence ratios (SIRs). We have included 95% confidence intervals (CIs) for these findings. If a 95% CI was not reported in the text, we have calculated approximate 95% CIs (Rothman and Boice 1979). In this article we generically refer to measures of association based on odds ratios and rate ratios as estimates of relative risk (RR). Many of the studies that we reviewed reported estimates of radiation dose to the bone marrow. We have included these values in the text in order to allow comparison of the magnitude of doses between study populations. We report radiation dose estimates in millisieverts. Some of the reviewed papers reported dose estimates in milligrays, a physical quantity describing

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