Relationship of Leukemia Risk to Radiation Dose Following Cancer of the Uterine Corpus

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Background: **Radiotherapy has been linked infrequently to secondary leukemia despite extensive exposure of the active bone marrow to ionizing radiation. Few studies include substantial numbers of elderly patients.** ***Purpose:*** **We evaluated women with cancer of the uterine corpus, the majority of whom were treated at older ages, to gain additional information on cancer risk following partial-body radiotherapy and to examine differences in risk between external-beam therapy and brachytherapy.** ***Methods:*** **A cohort of 110 000 women with invasive cancer of the uterine corpus who survived at least 1 year following their initial cancer was assembled from nine population-based cancer registries. Cancer diagnoses occurred from 1935 through 1985, and most patients were diagnosed during the 1960s and 1970s. Radiation doses were computed to 17 sections of the active bone marrow for 218 women who developed leukemia and for 775 matched control subjects.** ***Results:*** **Radiotherapy did not increase the risk of chronic lymphocytic leukemia (CLL) (relative risk [RR] = 0.90; 95% confidence interval [CI] = 0.4-1.9). However, for all leukemias except CLL, a significant risk was identified (RR = 1.92; 95% CI = 1.3-2.9). Overall, the pattern of risk in relation to dose was erratic and was most consistent with a constant increased risk across the entire dose range. The risk following continuous exposures from brachytherapy at comparatively low doses and low dose rates (RR = 1.80; 95% CI = 1.1-2.8; mean dose = 1.72 Gy) was similar to that after fractionated exposures at much higher doses and higher dose rates from external-beam treatment (RR = 2.29; 95% CI = 1.4-3.7; mean dose = 9.88 Gy), indicating a large difference in the estimated risk per unit dose. Risk did not vary by age at first exposure; increased risks were apparent for irradiated patients aged 65 years or older (RR = 1.77; 95% CI = 0.9-3.5).** ***Conclusion:*** **The leukemia risk associated with partial-body radiotherapy for uterine corpus cancer was small; about 14 excess leukemia cases were due to radiation per 10 000 women followed for 10 years. Women aged 65 years or older had a radiation risk comparable with that found in younger women. The relationship of leukemia risk to radiation dose was found to be complex due to the competing processes of cell killing, transformation, and repair. At very high doses delivered at high rates, destruction of cells likely dominates, and the risk per unit dose is low. In the low dose range, where dose was protracted and delivered at relatively low dose rates, the leukemia risk appears lower than that projected from risk estimates derived from the instantaneous whole-body exposures of atomic bomb survivors. [J Natl Cancer Inst 86:1315-1324, 1994]**

Ionizing radiation is an established human leukemogen (*1*). Notable increases in leukemia have been observed in atomic bomb survivors (*2*), radiologists (*3*), patients treated for malignant (*4,5*) and benign (*6-9*) diseases, and children exposed in utero to diagnostic x rays (*10*). Radiogenic leukemia has the shortest minimal latency of all cancers, appearing within about 2 years of exposure. The exposure–response relationship appears complex and depends on total dose to bone marrow, percent bone marrow exposed, and dose rate (dose/duration of exposure). Risk is higher among those exposed at younger ages; however, the risk among elderly populations has not been well studied. Among atomic bomb survivors who received an instantaneous whole-body exposure, the dose–response pattern appears linear-quadratic under about 4 Gy; above 4 Gy, the risk appears to fall or taper off (*1*).

Surprisingly, most studies of patients irradiated for cancer demonstrate either no or only a small leukemogenic effect. This small leukemogenic effect is most likely due to the substantial cell-killing effects from partial-body radiation exposures at such high levels. To provide additional information on leuke-

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See "Notes" section following "References."