

Radiation Dose and Leukemia Risk in Patients Treated for Cancer of the Cervix^{1,2}

John D. Boice, Jr.,^{3,4} Maria Blettner,^{3,5} Ruth A. Kleinerman,³ Marilyn Stovall,⁶ William C. Moloney,⁷ Göran Engholm,⁵ D. F. Austin,⁸ A. Bosch,⁹ D. L. Cookfair,¹⁰ E. T. Kremetz,¹¹ H. B. Latourette,¹² L. J. Peters,⁶ M. D. Schulz,¹³ M. Lundell,¹⁴ F. Pettersson,^{14,15} H. H. Storm,¹⁶ C. M. J. Bell,¹⁷ M. P. Coleman,¹⁸ P. Fraser,¹⁹ M. Palmer,²⁰ P. Prior,²¹ N. W. Choi,²² T. G. Hislop,²³ M. Koch,²⁴ D. Robb,²⁵ D. Robson,²⁶ R. F. Spengler,²⁷ D. von Fournier,²⁸ R. Frischkorn,²⁹ H. Lochmüller,³⁰ V. Pompe-Kirn,³¹ A. Rimpela,³² K. Kjørstad,³³ M. H. Pejovic,³⁴ K. Sigurdsson,³⁵ P. Pisani,³⁶ H. Kucera,³⁷ and G. B. Hutchison^{38,39}

ABSTRACT—To quantify the risk of radiation-induced leukemia and provide further information on the nature of the relationship between dose and response, a case-control study was undertaken in a cohort of over 150,000 women with invasive cancer of the uterine cervix. The cases either were reported to one of 17 population-based cancer registries or were treated in any of 16 oncologic clinics in Canada, Europe, and the United States. Four controls were individually matched to each of 195 cases of leukemia on the basis of age and calendar year when diagnosed with cervical cancer and survival time. Leukemia diagnoses were verified by one hematologist. Radiation dose to active bone marrow was estimated by medical physicists on the basis of the original radiotherapy records of study subjects. The risk of chronic lymphocytic leukemia, one of the few malignancies without evidence for an association with ionizing radiation, was not increased [relative risk (RR)=1.03; $n=52$]. However, for all other forms of leukemia taken together ($n=143$), a twofold risk was evident (RR=2.0; 90% confidence interval=1.0–4.2). Risk increased with increasing radiation dose until average doses of about 400 rad (4 Gy) were reached and then decreased at higher doses. This pattern is consistent with experimental data for which the downturn in risk at high doses has been interpreted as due to killing of potentially leukemic cells. The dose-response information was modeled with various RR functions, accounting for the nonhomogeneous distribution of radiation dose during radiotherapy. The local radiation doses to each of 14 bone marrow compartments for each patient were incorporated in the models, and the corresponding risks were summed. A good fit to the observed data was obtained with a linear-exponential function, which included a positive linear induction term and a negative exponential term. The estimate of the excess RR per rad was 0.9%, and the estimated RR at 100 rad (1 Gy) was 1.7. The model proposed in this study of risk proportional to mass exposed and of risk to an individual given by the sum of incremental risks to anatomic sites appears to be applicable to a wide range of dose distributions. Furthermore, the pattern of leukemia incidence associated with different levels of radiation dose is consistent with a model postulating increasing risk with increasing exposure, modified at high doses by increased frequency of cell death, which reduces risk.—*JNCI* 1987; 79: 1295–1311.

In human studies, leukemia has been found to be increased following radiation exposure more often than any other cancer (1–4). The active (red) bone marrow appears to be more sensitive to the carcinogenic action of ionizing radiations than any other tissue, and high

ABBREVIATIONS USED: AL= acute leukemia; AL+CML = acute leukemia of all types and chronic myelogenous leukemia; AML=acute myelogenous leukemia; CI=confidence interval; CLL=chronic lymphocytic leukemia; CML=chronic myelogenous leukemia; df=degrees of freedom; kVp=kilovolts peak; ML=maximum likelihood; PY-rad=person-years of observation multiplied by the average dose in rad; RR=relative risk.

¹ Received May 12, 1987; accepted July 13, 1987.

² Partially supported by Public Health Service contracts N01-CP11017, N01-CP01047, and N01-CP31035 with the Division of Cancer Etiology, National Cancer Institute.

³ Radiation Epidemiology Branch, Epidemiology and Biostatistics Program, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Bethesda, MD 20892.

⁴ Address reprint requests to Dr. Boice, Landow Building, Room 3A-22, National Institutes of Health, Bethesda, MD 20892.

⁵ International Agency for Research on Cancer, Lyon, France.

⁶ University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, TX 77030.

⁷ Harvard Medical School, Boston, MA 02115.

⁸ California Department of Health Services, Emeryville, CA 94608.

⁹ IGM Oncologic Hospital, Hato Rey, PR 00919.

¹⁰ Roswell Park Memorial Institute, Buffalo, NY 14263.

¹¹ Charity Hospital of Louisiana in New Orleans, Department of Surgery, New Orleans, LA 70112.

¹² Iowa Cancer Registry, Iowa City, IA 52242.

¹³ Massachusetts General Hospital, Boston, MA 02114.

¹⁴ Karolinska Hospital, Radiumhemmet, Stockholm 104 01, Sweden.

¹⁵ Swedish Cancer Registry, Stockholm 106 30, Sweden.

¹⁶ Danish Cancer Registry, DK-2100 Copenhagen, Denmark.

¹⁷ Thames Cancer Registry, Belmont, Sutton, Surrey SM2 5PY, England.

¹⁸ Imperial Cancer Research Fund, Cancer Epidemiology Unit, Radcliffe Infirmary, Oxford OX2 6HE, England.

¹⁹ Epidemiology Monitoring Unit, London School of Hygiene and Tropical Medicine, London WC1E 7HT, England.

²⁰ Christie Hospital and Radium Holt Institute, Manchester M20 9BX, England. Present address: ICI Pharmaceuticals PLC, Macclesfield, Cheshire SK10 4TG, England.

²¹ Cancer Registry, Epidemiology Research Unit, University of Birmingham, Birmingham B15 2TJ, England.

²² Manitoba Cancer Treatment Research Foundation and University of Manitoba, Faculty of Medicine, Winnipeg, MB R3E 0V9, Canada.

²³ Cancer Control Agency of British Columbia, Vancouver, BC, Canada.

²⁴ Cancer Registry, Alberta Cancer Board, Edmonton, AB, Canada.

RRs have been reported in patients treated with radiation for ankylosing spondylitis (5-7), benign gynecologic disorders (8, 9), tinea capitis (10), breast cancer (11-13), endometrial cancer (11, 13, 14), non-Hodgkin's lymphoma (15), and thyroid cancer (16). Recently, we reported for the first time in cervical cancer patients a significant 1.3-fold risk of leukemia of all types, except CLL, following radiotherapy (17). Atomic bomb survivors (18-20), American radiologists (21, 22), and children exposed prenatally to x-rays (23-25) also have been found to be at increased risk for leukemia development. Despite these numerous studies, the relationship between radiation dose and leukemia risk is not well understood. Only two exposed populations have provided information on leukemia risk over a wide range of bone marrow doses, the atomic bomb survivors (4, 18) and the British patients with spondylitis treated with radiotherapy (6). The uncertainties in dose estimation among atomic bomb survivors (26) raise questions as to the accuracy of the reported risk estimates. Similarly, the recent follow-up of spondylitics (6) was limited to patients who received only one treatment course, and the shape of the dose-response curve was erratic and consistent with

several different models, including one in which risk did not vary with dose.

Cervical cancer patients treated with radiation had been considered an excellent population to study for dose-response information because the exposures could be accurately quantified, large numbers were available for study, survival was relatively good, and patients treated by surgery alone could be evaluated for comparison (17, 27, 28). Surprisingly, several large investigations of cervical cancer patients have failed to find an excess of leukemia even close to the number anticipated based on current estimates of radiation risk (11, 14, 17, 27-31). A possible explanation for these unexpectedly smaller risks is that large therapeutic doses to substantial portions of bone marrow in the pelvic region kill marrow stem cells or render them incapable of division and so reduce the otherwise expected yield of leukemia (28, 32). (Throughout this article we use the term "cell killing" to refer to all processes that result in cell loss, such as cell death and cell inactivation.) However, in a large enough population of cervical cancer patients, the nonlethal low doses received by bone marrow residing outside the pelvis might provide additional information on the nature of the dependence of leukemia induction on radiation dose. A substantial increase in numbers could be obtained by combining our previous cancer registry investigation (17) with other hospital series (27). The larger population now studied has provided new information on the relationship between dose and leukemia induction and allows us to conclude that cancer incidence in humans following radiation exposure can be described as the result of competing processes of cancer induction and cell killing, varying independently with dose. Data presented in this paper were collected as part of a larger investigation to evaluate dose-response relationships for solid tumors as well, and other results will appear in a separate report.

MATERIALS AND METHODS

Study population.— The International Radiation Study of Cervical Cancer Patients evolved from a World Health Organization-sponsored investigation of 30,000 women treated for cervical cancer in 9 countries (27, 28). The study was expanded by including patients reported to population-based cancer registries, and results from initial cohort analyses have been published (17, 33). For several registries, the follow-up was extended and additional cases of leukemia were identified for this report. To provide new insights into radiation carcinogenesis and to increase the precision of current estimates of risk, a case-control study was conducted in the participating 17 registries and 16 clinics (table 1). The earliest reported treatment was in 1920, but most women were treated between 1940 and 1970. Cases were women with invasive cancer of the uterine cervix, treated with or without radiotherapy, who developed leukemia at least 1 year after the diagnosis of cervical cancer. Cases and controls were excluded if they had developed a cancer other than nonmelanoma skin cancer prior to the diagnosis of

²⁵ New Brunswick Provincial Tumor Registry, Saint John Regional Hospital, Saint John, NB, Canada.

²⁶ Saskatchewan Cancer Foundation, Regina, SK, Canada.

²⁷ Ontario Cancer Treatment and Research Foundation, Toronto ON M4H 1A8, Canada. Present address: Vermont Department of Health, Burlington, VT 05402.

²⁸ University Women's Clinic, 6900 Heidelberg, Federal Republic of Germany.

²⁹ Department of Gynecological Radiation, University Women's Clinic, 3400 Göttingen, Federal Republic of Germany.

³⁰ University Women's Clinic, Munich, Federal Republic of Germany

³¹ Slovenia Cancer Registry, Institute of Oncology, Zaloska 2, 6100 Ljubljana, Yugoslavia.

³² Finnish Cancer Registry, Liisankatu 21B, 00170 Helsinki 17 Finland.

³³ Norwegian Radium Hospital, Oslo 3, Norway.

³⁴ Gustave-Roussy Institute, Villejuif, France.

³⁵ Cancer Detection Clinic, Division of Gynecologic Oncology, Icelandic Cancer Society, IS-125 Reykjavik, Iceland.

³⁶ National Institute for Study and Treatment of Tumors, 20135 Milan, Italy.

³⁷ University Women's Clinic, 1090 Vienna, Austria.

³⁸ Harvard School of Public Health, Boston, MA 02115.

³⁹ We are grateful to the members of the eight working groups who have guided this study since its inception; to the steering committee members (Dr. George B. Hutchison, Dr. Hermann Lisco, and Dr. Brian MacMahon) for their active participation; to the dosimetry subcommittee (Marilyn Stovall, Dr. Marvin Rosenstein, and Dr. Goren Svensson) who provided expert advice and organ dose determinations; to Dr. Rudolfo Saracci, Dr. Peter G. Smith, Dr. Robin Mole, Dr. Mortimer M. Elkind, and Sir Edward E. Pochin who provided helpful advice; to Mr. Robert Weinstock for computer assistance; to Mr. Paul Hurwitz, Ms. Beth Kramer, and Ms. Danielle Magnin for data collection support; and to Ms. Mary Abraham for typing the manuscript. Most important, we are indebted to the staffs of the many participating oncology clinics, cancer registries, and medical facilities without whom this study would not have been possible

cervical cancer. Controls were chosen from the same clinic or cancer registry as the corresponding case. Four controls were matched to each case from the population of patients with invasive cervical cancer on the following criteria: *a)* diagnosed with invasive cervical cancer in the same 5-year age group as the case; *b)* diagnosed with invasive cervical cancer in the same calendar year as the case when possible, otherwise within 2 years; *c)* survived after diagnosis for at least as long as the period between the diagnosis of cervical cancer and the diagnosis of leukemia in the case; and *d)* did not develop a second cancer during this same time period. Leukemia cases and controls from cancer registry-reporting areas were readily selected using record-linkage procedures. For oncologic clinics, subjects first had to be followed forward in time to identify those who subsequently developed leukemia, as well as to describe the survival characteristics of the population available as controls. The extent of follow-up efforts varied by clinic, from relying solely on hospital records to sending questionnaires directly to the patients. Seventy-three valid leukemia diagnoses were identified from clinic records and 122 from cancer registries. Sixteen additional cases reported as leukemia were rejected after histological review (*see below*). Four controls per case were obtained for 175 cases, 3 for 7 cases, 2 for 11 cases, and 1 for 2 cases. Altogether, 745 controls were selected. Information on treatment for cervical cancer and demographic factors was abstracted for all study subjects from the records of the original hospital at which they were diagnosed or treated. Each center used the same abstract form and followed the same protocol for data collection. Hematologic information on leukemia diagnoses was obtained when available. Because of the complexity in abstracting radiotherapy records, photocopies were made and sent to the consulting medical physicist (M. S.) for review and detailed evaluation.

Ascertainment of hematologic disease.— All leukemia diagnoses were reviewed and classified by the study hematologist (W. C. M.). To assist in classification, blood smears, bone marrow smears or sections, and reports were obtained when available. Overall, 195 of 211 (92%) reported diagnoses of leukemia were confirmed: 52 as CLL, 17 as acute lymphocytic leukemia, 72 as AML, 41 as CML, 12 as AL not otherwise specified, and 1 myeloid leukemia not otherwise specified. Because CLL is one of the few malignancies not known to be increased following radiation exposure, the data were divided into two categories: CLL and all other leukemias. The latter category includes AL of all types and CML, i.e., all leukemias for which a radiation etiology has been demonstrated. Although limited by the small numbers of specific types of leukemia, an attempt was made to investigate separately the association between radiation and risk of AL and of CML.

Ascertainment of radiation dose.— Radiotherapy had been given by a variety of methods: external beam, brachytherapy using intracavitary isotope application, or a combination of both. Radium was the intracavitary source most frequently used; the goal of such treatment

TABLE 1.—Number of women with cervical cancer who developed leukemia and their controls, by clinic or cancer registry and treatment^a

Center No.	Center	Leukemia cases: Radiotherapy		Controls: Radiotherapy	
		Yes	No	Yes	No
Clinics					
1	Göttingen	2	0	6	2
4	Munich	4	0	16	0
9	Bologna	1	0	4	0
10	Hamburg	1	0	2	0
13	Vienna II	1	0	3	1
18	Boston	2	0	4	4
19	Houston	7	0	28	0
24	New Orleans	2	0	8	0
25	Heidelberg	4	0	16	0
26	Manchester	13	0	52	0
28	San Juan	1	0	4	0
29	Paris II	2	0	7	0
30	Baltimore	2	0	12	0
33	Stockholm	16	0	60	0
45	Buffalo	13	1	37	3
Registries					
50	Connecticut	13	1	43	10
52	Iowa	7	1	30	0
53	California	9	1	35	8
60	Denmark	25	2	91	17
61	Finland	6	0	24	0
62	Norway	4	0	16	0
63	Sweden	18	0	67	5
64	South Thames	4	1	19	1
65	Birmingham	4	1	18	0
70	New Brunswick	1	0	2	0
72	Ontario	5	0	19	0
73	British Columbia	3	0	12	0
74	Manitoba	1	0	3	1
75	Alberta	3	0	12	0
76	Saskatchewan	2	0	8	0
80	Slovenia	3	4	8	20
81	Iceland	2	0	6	0
	All centers	181	12	672	72

^aRadiation treatment was not known for 1 leukemia case (CML) from Baltimore, 1 leukemia case (AML) from California, and 1 control from Ontario.

was to deliver a very high dose to a very small volume of tissue surrounding the radium. The purpose of external beam therapy was to deliver a high radiation dose to the remainder of the pelvic contents, including the lymph nodes. Commonly used methods of radiotherapy for cancer of the uterine cervix varied over the years of the study and included the Stockholm, Manchester, and Fletcher systems (34). Low-stage disease was treated primarily with intracavitary radium in place for 36 hours or more; advanced disease was treated primarily with external beams during which fractions of about 200 rad (2 Gy) were delivered to the pelvis over several weeks. Over 70% of the patients studied were treated with both external beams and intracavitary applications. Commonly used external beam sources included orthovoltage x-ray machines (200–400 kVp), cobalt-60, and megavoltage machines, such as betatrons, van de Graaff generators, and linear accelerators. During more recent

TABLE 2.—Proportion of women with cervical cancer by calendar year of diagnosis and method of radiotherapy

Type of radiotherapy	Percent of women by year of cervical cancer diagnosis			
	<1950 (n=255)	1950-59 (n=220)	1960-64 (n=228)	≥1965 (n=237)
Orthovoltage, any, 200-400 kVp	64.7	60.5	34.7	9.7
Megavoltage, any ^a	0.0	8.2	36.8	59.1
External beam, type unknown	11.4	3.6	1.3	2.5
Brachytherapy only	19.7	18.2	16.4	14.8
External beam only	2.4	2.3	5.3	2.5
External beam and brachytherapy	74.8	70.0	68.1	69.1
None	3.1	9.5	10.1	13.5

^aIncludes cobalt-60, linear accelerators, van de Graaff generators, and betatrons.

years, orthovoltage machines were replaced almost entirely with megavoltage therapy units (table 2).

Most external beam treatments (51%) were given 5 days per week, although 37% of the treatments lasted 6 days per week. Sixty percent of treatments were completed in 30 days and 96% in 60 days.

A questionnaire concerning various machines and procedures used to treat cervical cancer patients over the wide range of years covered by the investigation was completed by radiotherapists or physicists at practically all participating medical facilities. Occasionally, visits to various treatment centers were made by the study physicist (M. S.). Radiation dose was then estimated to

14 individual segments of the bone marrow on the basis of individual patient treatment records, anthropometric factors, and specific sources of radiation treatment. Primary radiation to the pelvic area was considered, as was the radiation scattered from the patient's body or leakage through the collimator head of the external beam unit. Actual exposure situations were simulated, and dosimetry measurements were made on various water and anthropomorphic phantoms. Organ dose simulation calculations using Monte Carlo computer codes were also conducted (35). Two cases and 1 control could not be classified as to whether radiotherapy was given. Radiotherapy dose information was not available for 8 cases and 4 controls and was incomplete for 1 case and 15 controls. These cases and controls were excluded from all dose-response analyses. For all cases and controls with sufficiently comprehensive dosimetry information, the average dose to the 14 individual bone marrow segments is shown in table 3. The average dose to total bone marrow ($d = \sum_{i=1}^{14} w_i D_i$) was computed as the

sum of the dose to each anatomic site (D_i) multiplied by the proportion of active bone marrow (w_i) assumed to reside at that site (36). We refer to this weighted average dose throughout the text as the average or mean dose to the total bone marrow in the body. Additional dosimetry details can be found in Stovall (34).

Data analysis.—Comparisons between cases and individually matched controls with respect to radiation exposure were made using conditional logistic regression methods described in Breslow and Day (37). For

TABLE 3.—Distribution of active bone marrow and average dose per anatomic site from radiotherapy for cervical cancer

Anatomic site	Percent of active bone marrow, ^a $w_i \times 100\%$	Dose, D_i , to bone marrow, rad ^b			Weighted ^c dose to bone marrow for all radiotherapy, $w_i D_i$, rad	Percent contribution of $w_i D_i$ to mean dose to total marrow, 710 rad, %
		Brachytherapy only	External beam only	All radiotherapy		
Humeri	2.3	8	18	15	0.3	0.1
Clavicle	0.8	5	12	9	0.1	<0.1
Femur, top quarter ^d	3.4	380	470	580	19.7	2.8
Femur, second quarter ^d	3.4	110	182	190	6.5	0.9
Pelvis and sacrum	27.4	790	2,780	2,020	553.5	78.0
Ribs and sternum	19.2	31	35	41	7.9	1.1
Scapulae	2.8	13	17	18	0.5	0.1
Cranium	7.6	2	6	5	0.4	0.1
Mandible	0.8	2	8	5	0.0	<0.1
Lumbar vertebrae 1 and 2	4.6	95	277	240	11.0	1.6
Lumbar vertebrae 3 and 4	5.2	230	1,000	760	39.5	5.6
Lumbar vertebra 5	2.5	500	3,850	2,510	62.8	8.8
Thoracic spine	16.1	31	44	47	7.6	1.1
Cervical spine	3.9	2	8	5	0.2	<0.1
All bone marrow	100.0				710.0	100.0

^aThe percent active bone marrow was taken from Cristy (36).

^bThe average bone marrow dose was based on dosimetry estimates for cases and controls combined.

^cFor example, for the humeri the weighted dose is 0.3 rad = (0.023) × (15 rad). The weighted average dose to the total bone marrow is $d = \sum_{i=1}^{14} w_i D_i = 710$ rad.

^dThe femur was divided into four quarters. In the age range at which cervical cancer occurs, the lower half of the femur contains no active marrow (36).

dichotomous (yes/no) and categorical classification of radiation dose, the computer program of Lubin (38) was used to provide estimates of RRs and corresponding 90% CIs. Because radiation is known to cause leukemia, one-sided statistical tests were generally used. A 90% CI that does not embrace 1.0 implies that the RR is significantly different from unity at the 5% level on a one-sided test. Radiation dose to active bone marrow was grouped into categories, and computations of RR between each category and the unexposed reference category were made using dummy indicator variables for the categories. Conditional ML methods were also used to estimate the effect of radiation in different subgroups, as defined by the matching factors of age, latency, and calendar year. A univariate analysis included tests of homogeneity and tests of trend of the RRs over discrete categories of the variables of interest. A multivariate analysis was also conducted to adjust simultaneously for the possible effect modification of the matching factors on radiation risk.

Because the pattern of RRs over dose categories was clearly nonlinear, general RR functions for matched case-control studies were developed to model the observed pattern [cf. (39, 40)]. We were guided by the general dose-incidence relationship often applied to effects at the cellular level and in experimental settings (4, 41, 42),

$$I(D) = (a_0 + a_1^*D + a_2^*D^2) \exp(b_1D + b_2D^2),$$

where $I(D)$ is the incidence of leukemia associated with dose D , the a_i 's are coefficients for the linear-quadratic induction terms, and the b_i 's are coefficients for the exponential term representing a dose-dependent reduction in risk that would result in a downturn of risk at sufficiently high doses. The RR model is then defined as the ratio of leukemia incidence at dose D to the leukemia incidence for zero dose $I(0)$, i.e., the background rate,

$$RR(D) = I(D)/I(0).$$

The dose-response relationship for our case-control data was then modeled with an RR function that incorporated the dose to each anatomic component of the bone marrow for a given individual. The general equation was

$$RR(D_1, \dots, D_{14}) = \sum_{i=1}^{14} w_i RR(D_i) = \sum_{i=1}^{14} w_i (1 + a_1 D_i + a_2 D_i^2) \exp(b_1 D_i + b_2 D_i^2),$$

where i designates each of 14 different bone marrow masses, m_i is the mass comprising the i^{th} anatomic region of the bone marrow, D_i is the homogeneous dose

received by m_i , $w_i = m_i/M$, $\sum_{i=1}^{14} m_i = M$ comprises the

total mass of bone marrow in an individual $a_1 = a_1^*/a_0$, $a_2 = a_2^*/a_0$, and the RR associated with exposure to the i^{th} anatomic region is simply

$$RR(D_i) = (1 + a_1 D_i + a_2 D_i^2) \exp(b_1 D_i + b_2 D_i^2).$$

Throughout the remainder of this paper we use the term "incremental" risk to refer to the risk $RR(D_i)$ associated with exposure to a specific segment of the active bone marrow. The general RR function above implies that the total risk to an individual is the sum of incremental risks attributable to individually exposed masses of marrow. Further, it is assumed that marrow target cells do not move, or do not move much, from region to region during the course of treatment.

The method of conditional ML was used to estimate the parameters in the RR model. The log likelihood functions were maximized with Newton-Raphson methods to calculate the ML estimators. The log likelihoods over a range of parameter values were computed to confirm these results. Likelihood ratio tests were calculated, as were score statistics to test whether more complex models gave better fits to the observed data than simple linear ($a_2 = b_1 = b_2 = 0$) or exponential ($a_1 = a_2 = b_2 = 0$) RR models. The observed information matrix was used to obtain estimators for the standard errors of the parameters. These standard errors were not used to construct CIs because such intervals developed from normal distribution theory are of rather poor quality (43). A better approach to compute CIs is to calculate the log likelihoods over a grid of values of a and b and to construct a region of all values for which the log likelihoods differ by less than a designated amount from its maximum. These statistical considerations will be presented in a separate publication.

RESULTS

Characteristics of the 195 leukemia cases and their 745 controls are shown in table 4. The average age at cervical cancer diagnosis was 52 years, and the average age at leukemia diagnosis was 61 years for AL+CML, 62 years for AML, 64 years for acute lymphocytic leukemia, 60 years for CML, and 67 years for CLL. Half of the leukemia cases were diagnosed with cervical cancer prior to 1960, and half of the leukemia diagnoses occurred within 10 years of initial treatment for cervical cancer. The highest proportion of AL+CML occurred among the most recently treated cases, whereas CLL occurred most frequently among women treated prior to 1950. Most of the cases and controls had either stage I or stage II cervical cancer, and 70% were treated with both brachytherapy and external beam therapy. The most common external beam therapy was orthovoltage (58%), followed by cobalt-60 (22%), betatrons (7%), and other megavoltage units (6%). The weighted average dose to

the total bone marrow ($d = \sum_{i=1}^{14} w_i D_i$) was 710 rad

(7.1 Gy). Exposure to the pelvis and sacrum, lumbar spine, and femur contributed 78, 16, and 4%, respectively, of the average marrow dose. For women who received only brachytherapy, the average bone marrow dose was only 270 rad (2.7 Gy), and mean doses to indi-

vidual anatomic sites were uniformly lower than treatments including external beams (table 3). For the purposes of dose estimation, almost 90% of the radiotherapy records were judged by the consulting medical physicist to be of high quality. Cases and controls whose radiotherapy information was considered to be of low quality were excluded from the dose-response analyses and tabulations.

The RR for AL+CML associated with radiotherapy was 2.02, whereas no risk (RR=1.03) was apparent for CLL (table 5). There was a suggestion that the radio-

genic risk for CML (RR=4.2) was higher than for AL (RR=1.6). However, this difference was not significant, and the small number of unexposed leukemia cases precluded our ability to conduct further analyses of leukemia subtypes.

Risk for AL+CML was highest for those exposed under age 45 years and decreased with increasing age at radiotherapy (table 6). For cervical cancer patients over the age of 55 years when first treated with radiotherapy, little risk of AL+CML was apparent (RR=1.07; 90% CI=0.4-2.7). Practically all the excess risk occurred

TABLE 4.— Characteristics of women who developed leukemia following cervical cancer diagnosis and their matched controls

Characteristic	Leukemia cases, %				All controls, % (n= 745)
	AL+CML (n= 143)	CML (n= 41)	CLL (n= 52)	All types (n= 195)	
Age at diagnosis, yr					
<45	30.8	36.6	26.9	29.7	30.0
45-54	30.1	29.3	26.9	29.2	29.5
55-64	29.4	26.8	26.9	28.7	28.2
≥65	9.8	7.3	19.2	12.3	12.3
Time since diagnosis, yr ^a					
1-4	28.7	17.0	13.5	24.6	^a
5-9	32.9	36.6	26.9	31.3	^a
10-14	16.1	24.4	11.5	14.9	^a
15-19	9.1	12.2	23.1	12.8	^a
≥20	13.3	9.8	25.0	16.4	^a
Calendar yr of cervical cancer diagnosis					
<1950	24.5	26.8	38.5	28.2 ^b	23.9 ^b
1950-59	20.3	19.5	28.9	22.6 ^b	28.3 ^b
1960-64	23.1	29.3	26.9	24.1	23.8
≥1965	32.2	24.4	5.8	25.1	24.1
Stage of cervical cancer					
I	32.9	26.8	42.3	35.4	37.6
II	38.5	39.0	32.7	36.9	36.2
III-IV	8.4	4.9	11.5	9.2	14.2
Unknown	20.3	29.3	13.5	18.5	12.0
Type of radiotherapy					
External beam only	5.6	4.9	1.9	4.6	2.7
Brachytherapy only	17.5	19.5	17.3	17.4	17.1
External beam and brachytherapy	69.9	70.7	73.1	70.8	70.2
None	5.6	2.4	7.7	6.2	9.7
Missing or unknown ^c	1.4	2.4	0.0	1.0	0.3
Type of external beam ^d					
Orthovoltage, 200-400 kVp	51.9	51.6	71.8	57.1	58.2
Cobalt-60	24.1	25.8	18.0	22.4	21.9
Megavoltage	10.2	6.4	2.6	8.2	5.0
Betatron	2.8	6.5	5.1	3.4	8.5
Unknown	11.1	9.7	2.6	8.8	6.5
Surgical treatment	22.4	24.4	19.2	21.5	23.1
Radiotherapy for other conditions	6.3	2.4	15.4	8.7	7.3
Cervical cancer recurrence	6.0	2.6	5.9	6.0	8.4
Quality of radiotherapy information used for dosimetry					
Very good	67.8	73.2	73.1	69.2	71.5
Good, only minor problems	13.3	9.8	3.4	10.8	9.7
Fair, but major problems	7.0	4.9	11.5	8.2	6.4
Incomplete information	4.9	7.3	3.9	4.6	2.5
No or unknown radiation	7.0	4.9	7.7	7.2	9.8

^aFor the women who developed leukemia, this represents the interval between date of cervical cancer diagnosis and date of leukemia diagnosis. Each matched control lived at least as long as the case.

^bThe "apparent" discrepancy between the case and control distributions by calendar year is because many cases diagnosed with cervical cancer prior to 1950 had fewer than 4 controls and because some cases diagnosed in 1948 and 1949 were matched to controls diagnosed in 1950 and 1951. The matched analysis, which considered variable matching ratios, accounted for these apparent differences.

^cIncluded in this category are 1 woman known to have been treated with radiation but the modalities were not known and 3 women for whom radiation treatment was unknown.

^dPercentages apply only to women receiving external beam treatment.

TABLE 5.— RRs for different categories of leukemia associated with radiotherapy for cervical cancer

Type of leukemia	Radiotherapy	Numbers		Average dose to total bone marrow, ^a rad	RR, matched	90% CI
		Cases	Controls			
AL+CML ^b	Yes	133	489	720	2.02	1.0-4.2
	No	8	56			
CML	Yes	39	138	730	4.20	0.7-26
	No	1	13			
AL	Yes	93	348	710	1.63	0.7-3.6
	No	7	42			
CLL	Yes	48	183	670	1.03	0.3-3.9
	No	4	16			

^aThis is the average of a weighted mean dose to individuals. The mean dose to the total bone marrow for an individual *j* is $d_j = \sum_{i=1}^{14} w_i D_{ij}$. For subgroups of *n* women, the average of these mean doses is $(1/n) \sum_{j=1}^n d_j$.

^bTwo cases of AL+CML and 1 matched control could not be classified as to whether radiotherapy was given and were excluded from this analysis. One case of AL+CML was myeloid leukemia, not otherwise specified.

TABLE 6.— RR of AL+ CML associated with radiotherapy by age at diagnosis, time since diagnosis, calendar year of diagnosis of cervical cancer, and type of radiotherapy

Characteristic	Numbers ^a		Average dose to total bone marrow, rad ^b	RR, ^c matched	90% CI
	Cases	Controls			
Age at diagnosis, yr					
<45	43 (41)	169 (148)	690	4.62	0.8-28
45-54	42 (40)	162 (144)	710	3.09	0.8-12
55-64	42 (39)	161 (145)	750	1.36	0.5-4.0
≥65	14 (13)	53 (52)	730	0.25	0.002-2.5
Time since diagnosis, yr					
1-4	41 (40)	163 (137)	770	8.91	1.6-50
5-9	47 (43)	175 (158)	710	1.08	0.4-3.0
10-14	22 (20)	92 (84)	650	1.00	0.1-9.0
≥15	31 (30)	115 (110)	710	0.64	0.1-4.9
Calendar yr of cervical cancer diagnosis					
<1950	35 (34)	123 (116)	600	1.80	0.3-11
1950-59	29 (27)	116 (112)	730	0.38	0.1-2.2
1960-64	31 (29)	128 (112)	730	2.49	0.4-15
≥1965	46 (43)	178 (149)	790	3.13	1.1-9.2
Type of radiotherapy					
None	8 (0)	56 (0)	0	1.00	
Brachytherapy only	25 (25)	92 (92)	270	2.04	0.9-4.7
External beam only	8 (8)	15 (15)	890	3.87	1.4-11
External beam and brachytherapy	100 (100)	381 (381)	820	1.88	0.9-3.9

Stratum-specific analysis

Strata	Homogeneity test			Trend test		Comments
	Chi-square	df	P-value	Chi-square	P-value	
Age	4.34	3	0.23	2.80	0.09	Negative trend
Time	4.63	3	0.20	3.38	0.07	Negative trend
Calendar yr	3.37	3	0.34	0.74	0.39	No trend

Multivariate analysis

Variables	Maximum log likelihood	Score test		
		Chi-square	df	P-value
Radiation	-218.63			
Radiation + time	-216.17	4.63	3	0.20
Radiation + time + age	-214.56	4.39	3	0.22
Radiation + time + age + calendar yr	-213.18	3.41	3	0.33

^aNumber of exposed subjects is in parentheses.

^bAverage bone marrow dose computed only for those given radiotherapy and differs slightly from the values in table 3, which also includes cases of CLL and their matched controls. See also footnote a, table 5.

^cReference category is the unexposed.

TABLE 7.—RR of AL+CML computed using matched analysis for grouped data, grouped by bone marrow dose averaged over total body^a

Dose category, rad	Average bone marrow dose, rad ^b	Numbers		RR, matched	90% CI
		Cases	Controls		
0	0	8	56	1.00	R ^c
1-249	190	10	48	1.37	0.5-3.5
250-499	360	27	80	2.53	1.1-6.0
500-749	630	36	128	2.11	0.9-4.8
750-999	860	34	130	1.97	0.9-4.3
1,000-1,249	1,100	13	62	1.62	0.7-4.0
1,250-1,499	1,300	2	8	1.50	0.5-4.4
≥1,500	1,700	4	22	1.42	0.5-4.1

^a Numbers differ slightly from other tabulations because cases and controls with low-quality dosimetry information have been excluded here.

^b See footnote a, table 5.

^c R denotes reference category.

within 1-5 years after exposure. Risk also varied by calendar year of cervical cancer diagnosis, with the highest risk observed among women treated after 1965. The apparent greater risk among women treated after 1965, however, was an artifact attributable to different age and latency distributions; i.e., patients treated after 1965 had a higher proportion of women within 5 years of treatment and of women under age 55 years than patients treated in other calendar years. Subgroup analysis of the matching factors confirmed the decreasing risk with increasing age at treatment and time since treatment; however, including these variables in a multivariate analysis did not significantly improve the fit of the model beyond that provided by radiation alone.

Risk did not vary significantly by type of radiotherapy, although external beam therapy was associated with a fourfold risk. The higher risk for external beam therapy was not concentrated among patients treated with betatrons, for whom a small neutron component of the dose might have been more leukemogenic than treatments with lower energy machines, or among patients treated

with orthovoltage, for whom the dose to bone in the pelvic region would have been distributed differently than the dose from higher energy machines. Unfortunately, the small number of unexposed cases, only 8, precluded our ability to refine much further the analyses by type of radiotherapy.

The RR of radiogenic leukemia computed using a matched analysis for data grouped by dose appeared to rise until about 400 rad (4 Gy) (RR=2.5), when a downturn in risk was seen (table 7). The range of average dose to total bone marrow was broad, from about 100 to 2,500 rad (1-25 Gy). Various RR models were evaluated to learn whether the observed data could be represented adequately as some parametric function of dose (table 8). These models either incorporated the sum of the risks computed for each of 14 anatomical compartments of bone marrow or used the mean dose to total marrow as the regression variable. Based on radiobiological theory, a risk model incorporating a linear-quadratic induction term and an exponential "cell killing" term was investigated (4, 32, 42). The complete model, however, was too complex and contained too many parameters for the existing data set, and numerical problems arose that made convergence, and thus parameter estimation, difficult and not readily interpretable. The complete model, however, contains important nested models that could be evaluated and compared directly as to goodness of fit, such as the linear or additive model ($a_2 = b_1 = b_2 = 0$), the exponential or multiplicative model ($a_1 = a_2 = b_2 = 0$), a linear-exponential model ($a_2 = b_2 = 0$), and a quadratic-exponential model ($a_1 = b_2 = 0$). Both the linear-exponential and the quadratic-exponential models provided reasonable fits to the data. On the other hand, both the linear and the exponential models provided poor fits and could be rejected as unsuitable (text-fig. 1).

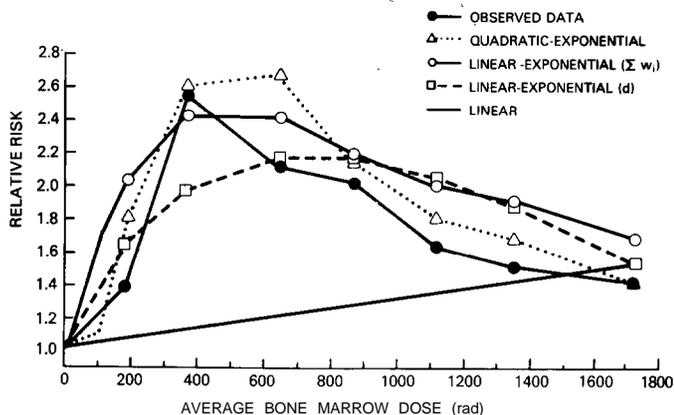
Text-figure 1 is a graphical representation of the various models fitted to the observed data. RR of AL+CML is plotted against mean dose to total bone marrow. For the observed data, the RRs represent a matched analysis for data grouped by dose. The RRs from the various

TABLE 8.—RR models and parameter estimates to describe the RR of AL+CML following radiotherapy for cervical cancer by dose^a

Dose-response model	Parameter estimates			
	$a_1 \times 10^{-3}$ (SE), rad ⁻¹	$a_2 \times 10^{-5}$ (SE), rad ⁻²	$b \times 10^{-4}$ (SE), rad ⁻¹	Maximum log likelihood
Null: RR=1.0	—	—	—	-205.90
Linear: $\sum_{i=1}^{14} w_i(1+a_1D_i)$	0.31 (0.45)	—	—	-205.55
Linear-exponential: $\sum_{i=1}^{14} w_i(1+a_1D_i)\exp(bD_i)$	8.8 (6.9)	—	-7.9 (3.4)	-203.85
Quadratic-exponential: $\sum_{i=1}^{14} w_i(1+a_2D_i^2)\exp(bD_i)$	—	2.5 (2.2)	-15 (3.5)	-203.28
Linear-exponential, mean marrow dose, d^b : ($1+a_1d$) $\exp(bd)$	5.2 (4.7)	—	-11 (5.3)	-204.63

^a D_i denotes the dose to the i^{th} bone marrow compartment ($i=1, \dots, 14$). w_i denotes the proportion of active bone marrow receiving dose D_i . The exponential correction is to account for cell death.

^b This model is based only on the mean dose to the total marrow ($d = \sum_{i=1}^{14} w_i D_i$), whereas the linear-exponential model above incorporates the sum of the risks computed for each of 14 anatomical compartments of bone marrow as the regression variable.



TEXT-FIGURE 1.—RRs of AL+CML were computed using a matched analysis for data grouped by average bone marrow dose ($d = \sum_{i=1}^{14} w_i D_i$), compared to fitted RRs from a linear-exponential model summing over anatomic components [$RR = \sum_{i=1}^{14} w_i (1 + a_1 D_i) \exp(b D_i)$], a linear-exponential model based on mean marrow dose [$RR = (1 + a_1 d) \exp(b d)$], a quadratic-exponential model [$RR = \sum_{i=1}^{14} w_i (1 + a_2 D_i^2) \exp(b D_i)$], and a linear model [$RR = \sum_{i=1}^{14} w_i (1 + a_1 D_i)$]. Coefficients used are from table 8. The plotted points were computed using the mean doses to 14 bone marrow compartments among women within the eight dose categories, grouped by average marrow dose.

models were computed using the mean doses to 14 anatomic bone marrow segments among women in the eight different dose categories. Although qualitative interpretations are readily made from the visual inspection of the graph, more quantitative inferences can be made by comparing the maximum log likelihoods found in table 8. Twice the difference between the maximum log likelihood of a particular model and the null model, i.e., the model representing no effect of radiation on leukemia incidence, is a chi-square statistic with the df equal to the difference between the numbers of estimated parameters in the test model and the null model. All models incorporating an exponential term to account for cell killing at high doses appear quite different from the null model, although not from each other.

The linear-exponential model summing incremental risks to individual bone marrow regions appeared to describe fairly well the observed pattern of risk over all dose categories (text-fig. 1). The estimated parameter, a_1 , can be interpreted as the excess RR per rad of radiation, i.e., 0.88% per rad, in the low-dose range where cell killing is negligible. The parameter b_1 indicates the reduction of risk as dose increases; e.g., 100 rad (1 Gy) would reduce the RR by 8%, 1,000 rad (10 Gy) by 55%, and 2,000 rad (20 Gy) by 79%. The RR at 100 rad (1 Gy) would be 1.7. In text-figure 2, the fitted RR of AL+CML for each woman derived under this model is plotted against her mean bone marrow dose. The range of RRs for similar average bone marrow doses is seen to be quite narrow.

Assuming that the bone marrow was uniformly exposed, the risk to an individual under the linear-exponential model would be simply

$$RR(D) = (1 + aD) \exp(bD),$$

where D now represents the same dose to each component of the bone marrow; i.e., $D = D_1 = D_2 \dots = D_{14}$ and $a = a_1$ and $b = b_1$. The risks for uniform dose distribution are also plotted in text-figure 2. The theoretical maximum dose for homogeneous bone marrow exposure is then

$$R R_{max} = (1 + aD_{max}) \exp(bD_{max}), \text{ with } D_{max} = -(a + b)/ab.$$

From our data, the theoretical maximum RR would be 4.5 and would occur at a theoretical whole-body dose of 1,150 rad (11.5 Gy). For $D > D_{max}$, the RR is seen to decrease with increasing dose (text-fig. 2).

For the quadratic-exponential model, the RR at 100 rad (1 Gy) would be estimated as 1.10, and the theoretical maximum RR for uniform bone marrow exposure would be 6.2 at 1,300 rad (13 Gy). Various other models were fit to the data, including functions of the logarithm of dose, but no model improved the fit. A function with a squared dose term in the exponential was fit to the data, as evaluated in some studies (4, 44, 45), but the results were similar to those obtained with models incorporating a linear term in the exponential and could not be distinguished by statistical methods. A function using the average dose to the total bone marrow ($d = \sum_{i=1}^{14} w_i D_i$) as the regression variable was also applied to the data,

$$RR(d) = (1 + ad) \exp(bd),$$

and the ML estimators for a and b were 0.0052 and -0.0011, respectively. At 100 rad (1 Gy), this model would predict an RR equal to 1.4. Comparisons with the observed data suggest that the risk of leukemia induction from the highly heterogeneous marrow exposure typical of cervical cancer treatment is reasonably well represented by a model that uses an average dose to total bone marrow (d) as the exposure variable. However, the risk estimators derived from this model differ from those obtained from the linear-exponential model incorporating incremental risks to individual anatomic sites of irradiated bone marrow, i.e., when the risks are computed for each of 14 bone marrow components for an individual and then are summed and evaluated over all individuals. The model based only on d yields biased estimates for the parameters a and b , because d is an average of very high and very low doses and because the underlying dose-response function is nonlinear. Thus the linear-exponential model incorporating incremental risks to individual bone marrow sites is to be preferred.

DISCUSSION

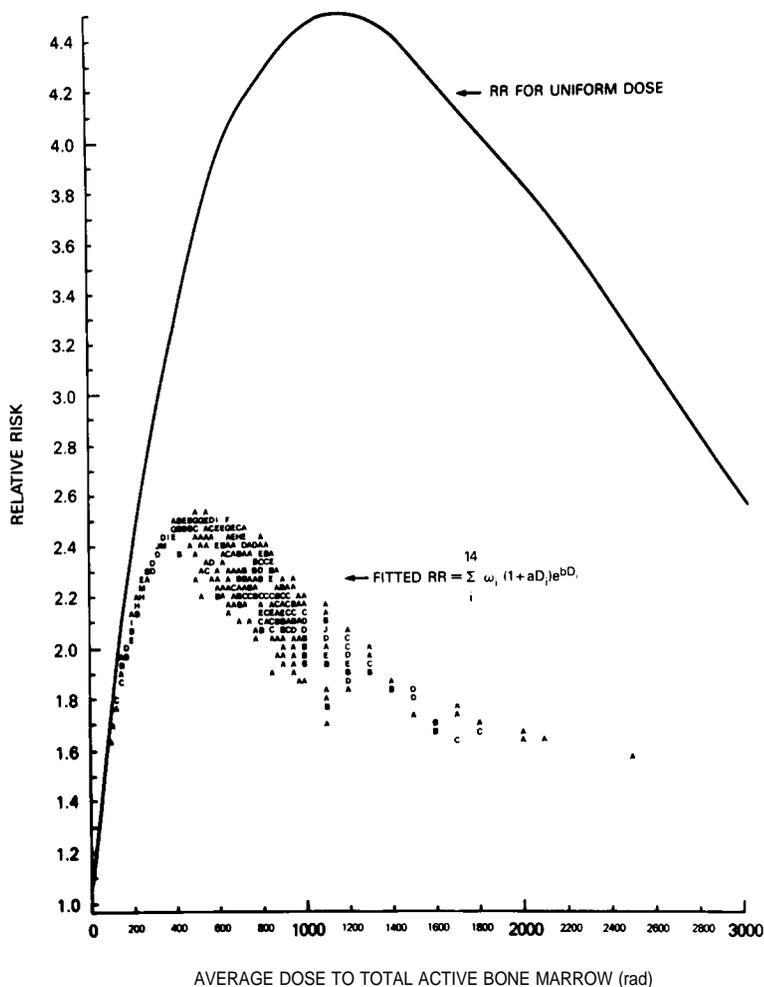
A twofold risk of AL+CML taken together was found following radiotherapy for cervical cancer. The absence

TEXT-FIGURE 2.—Fitted RR of AL+CML for each cervical cancer patient plotted against her mean bone marrow dose

(d). $RR = \sum_{i=1}^{14} w_i(1+a_1D_i)\exp(bD_i)$, where w_i is the proportion

of active bone marrow in anatomical area i , D_i is the homogeneous dose to the segment i , $a_1 = 8.8 \times 10^{-3} \text{rad}^{-1}$ and $b = -7.9 \times 10^{-4} \text{rad}^{-1}$, and $d = \sum_{i=1}^{14} w_i D_i$. Cases and controls

are not distinguished. Women with similar RR and mean dose are designated with letters, i.e., A represents 1 woman, B represents 2 women, C represents 3 women, and so on. Letters represent the fitted RR value for individuals exposed to certain mean doses averaged over the total bone marrow. Because women with similar mean doses could and did have different anatomic distributions of dose, a mean dose could be associated with different RRs. For comparison, the theoretical RR for uniform dose is also plotted, i.e., the RR assuming that each anatomic region i received the same dose $D = D_1 = \dots = D_{14}$.



of a radiation effect for CLL, one of the few malignancies that appears not to be increased following irradiation, suggests that there were no serious biases due to inaccuracies in the collection of data. Detailed reconstructions of the conditions of radiotherapy provided estimates of radiation doses to 14 different anatomical regions of the bone marrow for all individuals receiving radiation treatment. Risk of leukemia was seen to increase with increasing mean dose to the total bone marrow until about 400 rad (4 Gy), above which leukemia frequency was progressively reduced with increasing dose.

Linear-Exponential Model

A good fit to the observed data was obtained with a linear-exponential function for which the total risk to the individual was assumed to equal the sum of incremental risks to individually exposed masses of marrow. The incremental risk was taken to increase linearly with the mass exposed and inversely with the total mass of bone marrow in the individual. In addition, incremental risk was found to vary curvilinearly in a manner propor-

tional to a negative exponential in dose, which would reflect the ability of radiation to kill or render cells inactive at sufficiently high doses. The estimated relative increase in risk per rad, 0.9%, is consistent with the literature (2, 4), although the estimated RR at 100 rad (1 Gy) of 1.7 is about half the estimate from atomic bomb survivors, which included exposures at much younger ages (46).

The estimated individual RR for each mean marrow dose for all exposed women did not span a wide range (text-fig. 2), and this implies that the various dose distributions used in therapy for cervical cancer in this series represented only a limited range of possible dose distributions, all far from a uniform or homogeneous dose distribution. It is also apparent that, for any mean dose less than D_{\max} , an RR arbitrarily close to unity may be obtained by a highly heterogeneous dose distribution, such as when a large portion of marrow receives a negligible dose and a small portion of marrow receives a substantial dose. Thus the overall risks observed in our study of high-dose, partial-body irradiation would be expected to be much lower than those observed in subjects with whole-body irradiation as, for example, in the

survivors of the atomic bombings. Because pelvic marrow was probably destroyed or rendered inactive by large therapeutic exposures, cell killing may predominate over cell transformation at high doses (32, 47, 48) and thus explain why many fewer leukemias than expected, on the basis of current estimates of the risk of radiogenic leukemia, are observed in large cohorts of cervical cancer patients treated with radiotherapy (17).

Before these considerations came to light, it was thought paradoxical that women treated with high-dose radiation for malignant gynecological disease have been found to be at much lower risk of radiogenic leukemia than women treated with lower dose radiation for benign gynecological disorders (8, 9, 49). Both types of disease are treated with similar therapeutic modalities, and the anatomical sites of exposed bone marrow are comparable. The mean dose to the marrow is about 134 rad (1.34 Gy) for benign disease (9), in contrast to 710 rad (7.1 Gy) for malignant disease. The linear-exponential function, incorporating incremental risks from individual anatomic sites and accounting for cell death at high doses, provides a reasonable explanation for these apparently contradictory findings. Our analysis confirms the expectation that the higher radiation doses experienced during treatment for cervical cancer would result in substantially more cell killing and thus a lower leukemia risk than the small exposures used in therapy for benign gynecological disorders. Future comparisons applying the proposed model to studies of benign disease should provide more conclusive evidence on the adequacy of the linear-exponential function to describe risks over a wide range of doses (50).

Interestingly, radiation appears to be a somewhat limited leukemogen, with a maximum theoretical effect of about a 4.5-fold increase following uniform marrow exposure. Further, the highly heterogeneous marrow exposure resulting from radiotherapy for cervical cancer is much less efficient than a uniform exposure, with a maximum effect of only about a 2.5-fold increase (see text-fig. 2). In contrast, women of similar age treated for ovarian cancer with alkylating agents have experienced 100-fold increases of leukemia (51). These differences may be because of the greater sensitivity of cells to the killing or inactivation effects of radiation than for chemical agents.

A linear-exponential model relating risk to mean marrow dose (d), averaged over the entire body, appeared to fit the data reasonably well. Thus RR estimates for series of exposures that involve similar distributions of dose around the means may also be obtained using a linear-exponential model. Risk coefficients obtained from a model based only on d , however, should not be used for extrapolation to other populations for which the anatomic distribution of radiation dose is notably different. On the other hand, the linear-exponential model that relates risk to the doses to individual moieties of tissue appears to be generalizable to a wide range of dose distributions. We conclude that the concepts underlying this model, of risk proportional to mass exposed and of risk to an individual given by the sum of

incremental risks to anatomic sites, are biologically reasonable.

Other Models

Using the bone marrow dose averaged over the total body in the linear-exponential model (as opposed to summing the incremental risks from each of the 14 bone marrow sites) also provided a reasonable fit to the observed data. This was probably fortuitous because the dose distributions for cervical cancer patients with the same mean dose were so similar. A model based solely on mean dose to total marrow, however, would not give a useful fit for mixed data from studies of heterogeneous exposures and for uniform whole-body exposure. Further, the risk estimates from the mean dose model did differ somewhat from those considering incremental risks to individual anatomic bone marrow regions. The excess RR per rad was 0.53% (vs. 0.88%), and the theoretical maximum RR from uniform exposure was 2.2 (vs. 4.5), occurring at the estimated maximum effective dose for leukemia induction of 720 rad (7.2 Gy) versus 1,150 rad (11.5 Gy).

A linear-exponential model based on the mean dose to total marrow received by British patients treated with radiation for spondylitis provided an adequate fit to their observed data (6). The authors questioned the validity of the model, however, and were concerned that only a portion of the bone marrow was irradiated and that the fraction varied from patient to patient; e.g., one patient might receive intense radiotherapy only to the cervical spine, whereas another might receive treatment to the entire spine (7). Using the average marrow dose to the total body in the dose-response model may not be appropriate for combining data from such highly heterogeneous exposure circumstances. A better model would apply the exponential cell-killing term of each dose (D_i) to each bone marrow site and not just to the average dose (d) to total bone marrow.

The quadratic-exponential model relating the risk of leukemia to the square of radiation dose and accounting for the cell-killing effect of radiation provides a good fit to experimental data on radiation-induced myeloid leukemia in mice (52-54). This general class of models has also been applied to human data with the exponential term included (6, 47) and excluded (4). The exclusion of the term to account for cell killing was because of the belief that such an effect must be minimal in the low-dose range. Our data suggest, however, that it would be prudent to allow for the cell-killing effect of radiation on cells when predicting the leukemogenic effect of low doses of radiation. Further, while we could not distinguish statistically between the linear-exponential and the quadratic-exponential models, the risk estimates in the low-dose range differed appreciably. For example, the RR at 100 rad (1 Gy) was 1.1 for the quadratic-exponential function compared to 1.7 for the linear-exponential function. A quadratic response at low doses is similar to postulating a threshold effect, in that risk remains very small until rather substantial doses are

received. Because other human data based on atomic bomb survivors indicate threefold risks at 100 rad (1 Gy) (46), the quadratic-exponential model appears to underestimate substantially risks at low doses and results in estimates that are inconsistent with observation. Also, the quadratic-exponential model was found not to fit the data from British spondylitis patients treated with radiotherapy with the use of the average dose (d) to total bone marrow as the independent variable (6).

A linear dose-response relationship was clearly inconsistent with our data, as were other models that did not adjust for the decreased probability of cell survival at high doses. Mathematical models used to fit dose-response data for induction of breast cancer have included a linear induction term and an exponential cell-killing term with a dose-squared coefficient (4, 44, 45). However, since no cell survival response depending solely on the square of dose is known (52), we chose not to pursue this model beyond noting that it did provide an adequate fit to the observed data.

It should be noted that our general dose-response model implies that very high doses would result in an RR less than unity, i.e., sufficiently high doses of radiation would actually protect against leukemia induced by other causes. An alternative model considered was

$$RR(D_1, \dots, D_{14}) = \sum_{i=1}^{14} w_i [1 + aD_i \exp(bD_i)]$$

for which the RR would approach unity as dose approached infinity. Neither model could be distinguished statistically, and there was no evidence from text-figure 2 that the actual doses experienced by cervical cancer patients were large enough to produce an RR less than 1. Further, there is experimental evidence that radiation can, in fact, reduce the incidence of leukemia to a level below that seen spontaneously (55). Since the purpose of radiotherapy is to kill cancer cells, it seemed reasonable to retain the background rate in our RR model and thus permit radiation to kill premalignant leukemia cells transformed by other causes.

Finally, we also evaluated a linear-quadratic-exponential model of the form

$$RR(D_1, \dots, D_{14}) = \sum_{i=1}^{14} w_i [1 + aD_i + (a/X)D_i^2] \exp(bD_i)$$

for which the coefficient for the dose-squared induction term was assumed to be equal to the linear induction coefficient divided by the so-called crossover dose X (2, 4). The crossover dose is the dose for which the risk associated with the linear induction term equals the risk associated with the quadratic induction term. Analyses of leukemia data among atomic bomb survivors have estimated the crossover dose to be 116 rad (1.16 Gy). Interestingly, the maximum log likelihood and the dose-specific risk estimates computed from this linear-quadratic-exponential model were very similar to those from the linear-exponential model. The estimators for a and b were 0.0021 and -0.0015 , respectively.

Fractionation Effect

Not only did cervical cancer patients receive partial-body exposures that resulted in widely different doses to different regions of the bone marrow, but also the dose was delivered in fractions over a period of time that could span up to 8 weeks. For brachytherapy, radium could be implanted in the uterus and continuous exposure received for up to 3 days. In addition, 100-200 rad (1-2 Gy) to the pelvic region could have been delivered by external beams each day, 5 days per week for 4-6 weeks on average. While an approach was presented to account for the heterogeneous nature of the dose distributions within individual patients, we were unable to evaluate the influence of the protracted and complex nature of the treatments. Partitioning doses over time has been found to decrease the risk of leukemia in experimental animals (41, 56, 57), and dose-independent or flat dose-response curves have been reported in both cellular (58, 59) and animal (52, 56) studies qualitatively similar to the British spondylitis investigation. Elkind et al. (58) have postulated that repair of both sublethal cellular lesions at high doses and potentially transforming cellular lesions at low doses could contribute to the relatively flat dose-response curves observed when exposures are protracted over time. Data from some human leukemia cell lines suggest that repair of sublethal damage may occur, although investigations of rodent cells indicate that marrow stem cells, in large part, have a relatively small capacity for repair of this type of injury (60). Interestingly, Mole et al. (52, 56) argue that protraction should increase rather than decrease risk of leukemogenesis (as seen in human and experimental settings), because of its effect on increasing the number of transformable cells; i.e., cell inactivation is reduced by protraction and, during the period of radiation exposure, cell division of stem cells should be augmented by physiological feedback systems. If repopulation did occur, its effect would be qualitatively similar to the repair of sublethal damage, i.e., increasing the number of cells at risk and widening the shape of the dose-response curve.

The combined effects of repair of sublethal damage and repopulation following protracted exposures would be to make $1/b$, i.e., the dose (D_0) necessary to result in 63% cell inactivation, to be larger than that observed following single brief exposures. The value for $1/b$ from the various models (table 8) ranges from 660 to 1,270 rad (6.6-12.7 Gy), whereas comparable values for mouse and human stem cells in vitro are about 100 rad (1 Gy) (60). This difference of about tenfold suggests that cell replacement by division during prolonged periods of exposure plus repair of sublethal damage could contribute to the observed data and possibly to the "tailing" or plateauing of the effect suggested at very high doses. Thus the computed b for protracted exposure may actually represent some complex function of cell killing of primitive marrow cells, cell replacement by cell division, cell repair of sublethal damage, and time. Unfortunately, even with our large series of cervical cancer

patients we are unable to address the issue of dose protraction directly. Although it appeared that modeling the dose response by summing the incremental risks to various segments of bone marrow adequately described the observed data, fractionation may have influenced the slope of the dose response by broadening the induction curve and lowering the maximum. For all these reasons, the protracted nature of radiotherapy for cervical cancer may also have contributed to the lower overall risks as compared to single exposure situations such as among the atomic bomb survivors (46).

Comparisons With Other Studies

Similar to the British mortality study of spondylitics receiving radiotherapy to the spine (5-7, 61), the maximum risk of radiogenic leukemia occurred in the interval 1-5 years after initial treatment with radiotherapy. However, the pattern of risk over time differed from the studies of spondylitic patients and atomic bomb survivors (18) in that little radiation excess was apparent beyond 10 years after the initial treatment with radiation for cervical cancer. Although the wave-like patterns of risk over time were qualitatively similar, risk extended to at least 20 years after exposure in the other series.

The risk of leukemia following radiation treatment for cervical cancer was highest for those under 45 years of age at exposure, and the risk decreased with increasing age at irradiation. Among women over age 55 when treated, no radiation risk was evident. This pattern of age-specific risks also differs from the atomic bomb survivor studies in that while RRs decreased with increasing age at exposure, at older ages the RRs remained roughly constant (18). For the irradiated spondylitics, the RRs by age at exposure were seen to be relatively constant (6). Smith and Doll (6) have argued that the constancy of the RR by age at exposure suggests that radiation may interact with other factors that cause leukemia in a fashion consistent with a multiplying of underlying rates. The data from cervical cancer patients do not appear consistent with this supposition; however, the decreasing RR with age at treatment may be an artifact associated with our inability to estimate accurately the percent of active bone marrow in elderly women. If the percent distribution continues to change with age and becomes concentrated in the trunk marrow, then proportionally more cell killing of stem cells would be anticipated among older women than among younger women, and the risk of radiogenic leukemia would be seen to decrease with age at exposure. Finally, Ichimaru et al. (18) have suggested that the latent period for radiogenic leukemia increases in a manner proportional to the age at the time of exposure. We found no evidence to support this finding.

The overall dose-response relationship for cervical cancer patients differs from that previously reported from the atomic bomb survivor studies in which linear or linear-quadratic functions appeared consistent with the observed data (2, 4, 18, 46, 62). However, the recent

changes in dosimetry have apparently affected the shape of the dose-response relationship for leukemia (63). A downturn in risk among those exposed to 400 rad (4 Gy) is now observed, although this decrease may have been affected somewhat by biases in the dosimetry assessment for high-dose survivors coupled with differential survival. Interestingly, while most of the evidence for a radiation effect among the Japanese atomic bomb survivors occurred among those receiving more than 100 rad (1 Gy), the overall mean dose was only about 16 rad (0.16 Gy) (64). Recently, the linear-quadratic relationship between dose and cancer incidence was used to estimate risks following low doses of ionizing radiation (2). However, if cell killing has influenced the observed rates following exposures of more than 100 rad (1 Gy), then extrapolation from high-dose data to low-dose risks may not be strictly valid.

The first dose-response relationship reported from the study of British spondylitics was consistent with linearity (7). Subsequent publications excluded large numbers of patients who received more than one course of treatment, as well as more than half the reported leukemias, and there was no clear evidence to support any particular dose-response model (6). The average dose to total bone marrow was computed at 321 rad (3.21 Gy), and models to account for cell killing were fit to the observed data. The small number of leukemias, only 28, probably precluded the ability to distinguish clearly between various dose-response models. Further, accounting for incremental risks to individual skeletal components of the bone marrow might have sharpened the dose-response evaluation. A recent survey of leukemia following treatment for childhood cancer also failed to find evidence of a dose response over a wide range of average doses to the total active bone marrow [mean=1,000 rad (10 Gy)] (65). Once again, however, the number of leukemias, only 25, was small.

Among atomic bomb survivors the estimated RR of death due to leukemia was 3.95 at 100 rad (1 Gy), and the excess risk per million persons per year per rad was 1.51 (46). For men and women the RRs were similar at 100 rad (1 Gy), 3.8 and 4.1, respectively, but the absolute risks differed significantly, 1.95 vs. 1.20×10^{-6} PY-rad. Among spondylitis patients treated with radiation therapy, the overall RR was 5.9 and did not vary appreciably by dose. The overall excess in leukemia deaths was 0.59×10^{-6} PY-rad. Among cervical cancer patients, the RR of leukemia incidence was estimated to be 1.7 at 100 rad (1 Gy), and the absolute risk could be crudely approximated as 0.48×10^{-6} PY-rad [from $(RR-1) I/D$ (66), where RR was 1.7 at dose D equal to 100 rad (1 Gy) and I was the expected annual incidence of leukemia in the cervical cancer population estimated from the cohort study as 6.9×10^{-5}].

In comparing our results with those from other studies, the differences in the populations and exposure situations should be kept in mind. The atomic bomb survivors received an instantaneous exposure to the entire body. Men, women, and children were evaluated, and while the total numbers studied were over 100,000,

only 6,035 received more than 100 rad (1 Gy) and 25,202 over 10 rad (0.1 Gy) (64), and the dosimetry is currently undergoing major revisions (26). Total-body exposures of more than 600 rad (6 Gy) would have been lethal in most instances. Approximately 158 leukemia deaths have been reported to date among those exposed to more than 1 rad (46). "An important feature of the Hiroshima and Nagasaki experience is that, in fact, the largest part of the energy released by the bombs was in the form of heat and blast. Many of the survivors were burned, either by radiant heat from the fire-ball or by the fires that engulfed the cities directly after the bombings. Homes were destroyed; food was short; living patterns were profoundly disrupted. The influence of this concatenation of disasters upon the subsequent health of the survivors is unknowable. The issue is further complicated by the possibility that, at least to some degree, the less hardy members of the population had higher mortality during the first few weeks after the bombings, from either disease or radiation effects. Thus the survivors may on the one hand be selected as among the most fit of the bombed population but on the other hand have suffered a variety of experiences all combining to reduce their future fitness" (66).

The spondylitics were mainly men who, similar to women treated for cervical cancer, received fractionated and high-dose treatments to various anatomical regions of bone marrow. Such exposures, if received over the entire body, would have caused death in most individuals. Treatments occurred between 1935 and 1954. Although treatment was for a potentially debilitating disease, the disease itself did not appear associated with leukemia in the absence of radiation (67). Only mortality analyses based on death certificate information were performed, and the number of leukemias in the last report was small. It is also possible that some of the drugs commonly used to treat spondylitis, e.g., phenylbutazone, contributed to the leukemia excess (5).

The cervical cancer patients were treated for a life-threatening disease, and much higher doses were received than in the studies of atomic bomb survivors and spondylitics. Incident cancers rather than cancer deaths were evaluated, and the number of leukemias, 195, was large. Treatments occurred between 1920 and 1969, with higher doses tending to occur in the later years from the more modern modalities of radiotherapy. Many women did not survive the disease, especially those with more advanced disease who received the highest average doses to total bone marrow, i.e., more than 900 rad (9 Gy). Mostly older women were studied, with many more persons exposed over age 50 years than in the other two series. In the absence of radiotherapy, cervical cancer patients have not been found to be at increased risk of leukemia (17). Alkylating agents, potent leukemogens (51), are rarely given to treat cervical cancer, and thus this potentially confounding exposure is not a factor in this series. Very few women received mean doses to total marrow under 100 rad (1 Gy), so low-dose risks could not be evaluated directly.

Cautions in Interpretation

In addition to the unique circumstances of dose fractionation, age at exposure, and anatomic distribution of radiation dose in patients treated for cancer of the uterine cervix, other factors should be considered when interpreting and generalizing the findings from our study. All leukemias, other than CLL, were combined for most analyses, and while this was necessary because of the difficulties in analyzing smaller subgroups, it may not be valid if the dose-response relationships differ appreciably for the various types of leukemia (47, 68). Acute lymphocytic leukemia, for example, was infrequently induced among atomic bomb survivors exposed after age 20 (18), and only two deaths were attributed to this type of leukemia among British spondylitis patients given radiotherapy (5). Seventeen cases of acute lymphocytic leukemia were included in our analyses. Additional radiotherapy received by approximately 6% of all patients after the primary therapy was not considered in the dose-response modeling. However, when the data were analyzed adjusting for subsequent therapy, the RR of leukemia differed only slightly. Many of the subgroup analyses, e.g., by age at exposure, were limited because of the small number of unexposed cases (only 12 in total), and precise estimates of risk were precluded. Because radiotherapy was the treatment of choice for invasive cervical cancer for almost 80 years and because control selection within clinics was restricted to women of similar age and calendar year of diagnosis, it was possible that "overmatching" could have forced the exposures to be so similar that the effect of treatment could not be distinguished. However, there was sufficient variation of radiotherapy modalities by stage of disease that a wide range of bone marrow doses was observed. Further, risk estimates from the clinics in North America and Europe (for which the potential problem of overmatching would be most severe) were similar to those from the cancer registries (for which many hospitals in the reporting region were available for control selection), although the small numbers from Canadian registries did not indicate an elevated risk. Thus it appears unlikely that cases and controls were seriously overmatched with respect to radiation exposure.

Despite the large number of leukemias available for analysis, numerical problems arose when we tried to fit dose-response functions with more than two parameters to estimate. While we highlighted the linear-exponential response, other models with similar or additional parameters could not be rejected, although a linear dose-response model clearly was not consistent with the observed data. The univariate analysis presented in table 6 further suggested that risk decreased both with age at treatment and with time since treatment. Conceivably, the dose-response relationship might be sharpened by incorporating some of these parameters in the various models. Multivariate regression modeling of the RR by dose, allowing simultaneously for age at diagnosis and time since diagnosis, did not result in improved

parameter estimates or better discrimination between the various risk models. Further restricting the analysis to only those women within 5 years of treatment, however, did result in statistically significant differences between the null model of no effect and the linear-exponential and the quadratic-exponential models. For this 5-year latency analysis, the parameter estimates for the linear-exponential model were $a_1=0.021 \text{ rad}^{-1}$ and $b = -3.2 \times 10^{-4} \text{ rad}^{-1}$; for the quadratic-exponential model, they were $a_2=4.0 \times 10^{-5} \text{ rad}^{-2}$ and $b = -8.7 \times 10^{-4} \text{ rad}^{-1}$. We chose to include all ages and time intervals in the dose-response models, however, to be consistent with other epidemiologic studies. Both the atomic bomb survivors and patients treated for spondylitis, for example, were at significant risk when exposed after age 55 years and for time intervals beyond 5 years of follow-up (5, 46).

Because dose estimates were made for a wide range of therapy machines and isotope sources over many years and in many countries, errors in the estimated marrow doses could have arisen. Analysis of the data by quality of abstracted information, however, failed to change the RR appreciably. Possible biases in the collection of dosimetry data are assumed to be minimal, because the RR associated with radiotherapy for CLL was 1.03 and consistent with current knowledge that this disease is not increased following radiation exposure. It is also possible that additional division of the 14 anatomical bone segments could modify the study findings. The dose stated for each bone segment is an arithmetic average, although for bones close to the cervix, the dose distribution is clearly nonuniform. The exponential correction factor for cell killing varies nonarithmetically with dose, and the effect of representing a highly nonuniform distribution with an average dose would be to overestimate the contribution of the anatomic site to leukemia induction. Further subdividing the pelvis, lumbar spine, and femur could conceivably result in different risk estimates and model fits. Unfortunately, limitations in the radiation dosimetry preclude any further partitioning of these bones that received direct radiation exposure.

Differences between our case-control findings and our registry cohort analyses in terms of the magnitude of the RRs (RR=2.0 vs. RR=1.3) could be due to the increased sample size of the current investigation, which included additional registry years of follow-up and many more clinics, and to misclassification of treatment in registry records. Women who developed leukemia and were classified as unexposed in some cancer registry files were more likely to have received radiotherapy than women who were similarly classified but who did not develop leukemia (29, 33). Finally, the actual distribution of active bone marrow in normal adults is not well defined, and it is conceivable that the choice of different percentages of active bone marrow for anatomic sites could have changed the shape of the dose-response relationship. Reanalyzing the data using the distribution of Ellis (69), however, did not affect the shape of the curve or the estimates of risk appreciably, although it is conceivable that other distributions might. The probable

change in the distribution of active bone marrow in the body with increasing age (which we were unable to account for) could conceivably explain partially the decreasing risk of leukemia with increasing age at exposure observed in our data.

REFERENCES

- (1) MILLER RW, BEEBE GW. Leukemia, lymphoma, and multiple myeloma. In: Upton AC, Albert RE, Burns FJ, et al., eds. Radiation carcinogenesis. New York: Elsevier, 1986:245-260.
- (2) RALL JE, BEEBE GW, HOEL DG, et al. Report of the National Institutes of Health ad hoc working group to develop radio-epidemiological tables. Washington, DC: U.S. Govt Print Off, 1985 [DHHS publication No. (NIH)85-2748].
- (3) BOICE JD JR, FRAUMENI JF JR, eds. Radiation carcinogenesis: Epidemiology and biological significance. New York: Raven Press, 1984:1-489.
- (4) National Academy of Sciences Committee on the Biological Effects of Ionizing Radiations. The effects on populations of exposure to low levels of ionizing radiation: 1980. Washington, DC: Natl Acad Press, 1980:1-524.
- (5) DARBY SC, DOLL R, GILL SK, et al. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. *Br J Cancer* 1987; 55:179-190.
- (6) SMITH PG, DOLL R. Mortality among patients with ankylosing spondylitis after a single treatment course with x rays. *Br Med J* 1982; 284:449-460.
- (7) COURT BROWN WM, DOLL R. Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis. *Med Res Counc Spec Rep (London)* 1957; 295:1-135.
- (8) WAGONER JK. Leukemia and other malignancies following radiation therapy for gynecological disorders. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: Epidemiology and biological significance. New York: Raven Press, 1984: 153-159.
- (9) SMITH PC, DOLL R. Late effects of X irradiation in patients treated for metropathia haemorrhagica. *Br J Radiol* 1976; 49:224-232.
- (10) RON E, MODAN B, BOICE JD JR. Mortality from cancer and other causes following radiotherapy for ringworm of the scalp. *Am J Epidemiol*. In press.
- (11) BOVIN J-F, HUTCHISON GB, EVANS FB, et al. Leukemia after radiotherapy for first primary cancers of various anatomic sites. *Am J Epidemiol* 1986; 123:993-1003.
- (12) FISHER B, ROCKETTE H, FISHER ER, et al. Leukemia in breast cancer patients following adjuvant chemotherapy or postoperative radiotherapy: The NSABP experience. *J Clin Oncol* 1985; 3:1640-1658.
- (13) CURTIS RE, HANKEY BF, MYERS MH, et al. Risk of leukemia associated with the first course of cancer treatment: An analysis of the Surveillance, Epidemiology, and End Results Program experience. *JNCI* 1984; 72:531-544.
- (14) CURTIS RE, HOOVER RN, KLEINERMAN RA, et al. Second cancer following cancer of the female genital system in Connecticut, 1935-82. *Natl Cancer Inst Monogr* 1985; 68:113-137.
- (15) GREENE MH, YOUNG RC, MERRILL JM, et al. Evidence of a treatment dose-response in acute nonlymphocytic leukemias which occur after therapy of non-Hodgkin's lymphoma. *Cancer Res* 1983; 43:1891-1898.
- (16) EDMONDS CJ, SMITH T. The long-term hazards of the treatment of thyroid cancer with radioiodine. *Br J Radiol* 1986; 59:45-51.
- (17) BOICE JD JR, DAY NE, ANDERSEN A, et al. Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. *JNCI* 1985; 74:955-975.
- (18) ICHIMARU M, ISHIMARU T, BELSKY JL. Incidence of leukemia in atomic bomb survivors belonging to a fixed cohort in Hiroshima and Nagasaki, 1950-71: Radiation dose, years after exposure, age at exposure, and type of leukemia. *Jpn Radiat Res*

- 1978; 19:262-282.
- (19) LANGE RD, MOLONEY WC, YAMAWAKI T. Leukemia in atomic bomb survivors. I. General observations. *Blood* 1954; 9:574-585.
- (20) FOLLEY JH, BORGES W, YAMAWAKI T. Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. *Am J Med* 1952; 13:311-321.
- (21) MATANOSKI GM, SELTNER R, SARTWELL PE, et al. The current mortality rates of radiologists and other physician specialists: Specific causes of death. *Am J Epidemiol* 1975; 101:199-210.
- (22) LEWIS EB. Leukemia, multiple myeloma and aplastic anemia in American radiologists. *Science* 1963; 142:1492-1494.
- (23) HARVEY EB, BOICE JD JR, HONEYMAN M, et al. Prenatal x-ray exposure and childhood cancer in twins. *N Engl J Med* 1985; 312:541-545.
- (24) MONSON RR, MACMAHON B. Prenatal x-ray exposure and cancer in children. In: Boice JD Jr, Fraumeni JF Jr, eds. *Radiation carcinogenesis: Epidemiology and biological significance*. New York: Raven Press, 1984:97-105.
- (25) STEWART A, WEBB J, HEWITT D. A survey of childhood malignancies. *Br Med J* 1958; 1:1495-1508.
- (26) MARUYAMA T. Atomic bomb dosimetry for epidemiological studies of survivors in Hiroshima and Nagasaki. *Gann Monogr Cancer Res* 1986; 32:9-28.
- (27) BOICE JD, HUTCHISON GB. Leukemia in women following radiotherapy for cervical cancer. Ten-year follow-up of an international study. *JNCI* 1980; 65:115-129.
- (28) HUTCHISON GB. Leukemia in patients with cancer of the cervix uteri treated with radiation. A report covering the first 5 years of an international study. *J Natl Cancer Inst* 1968; 40:951-982.
- (29) STORM HH, BOICE JD JR. Leukaemia after cervical cancer irradiation in Denmark. *Int J Epidemiol* 1985; 14:363-368.
- (30) KLEINERMAN RA, CURTIS RE, BOICE JD JR, et al. Second cancers following radiotherapy for cervical cancer. *JNCI* 1982; 69:1027-1033.
- (31) SIMON N, BRUCER M, HAYES R. Radiation and leukemia in carcinoma of the cervix. *Radiology* 1960; 74:905-911.
- (32) GRAY LH. Radiation biology and cancer. In: *Cellular radiation biology*. M. D. Anderson Hospital and Tumor Institute. Eighteenth symposium on fundamental cancer research. Baltimore: Williams & Wilkins, 1965:7-25.
- (33) International Radiation Study Group on Cervical Cancer. Second cancer in relation to radiation treatment for cervical cancer. In: Day NE, Boice JD Jr, eds. *IARC Sci Publ* 1983; 52:1-207.
- (34) STOVALL M. Organ doses from radiotherapy of cancer of the uterine cervix. *IARC Sci Publ* 1983; 52:131-136.
- (35) ROSENSTEIN M. Organ doses in diagnostic radiology. Washington, D.C.: U.S. Govt Print Off, 1976 [DHEW publication No. (FDA)76-8030].
- (36) CRISTY M. Active bone marrow distribution as a function of age in humans. *Phys Med Biol* 1981; 26:389-400.
- (37) BRESLOW NE, DAY NE. Statistical methods in cancer research. Vol 1. The analysis of case-control studies. *IARC Sci Publ* 1980; 32:1-338.
- (38) LUBIN JH. A computer program for the analysis of matched case-control studies. *Comp Biomed Res* 1981; 14:138-143.
- (39) STORER BE, WACHOLDER S, BRESLOW NE. Maximum likelihood fitting of general risk models to stratified data. *Appl Statist* 1983; 32:172-181.
- (40) THOMAS DC. General relative risk models for survival time and matched case-control analysis. *Biometrics* 1981; 37:673-686.
- (41) United Nations Scientific Committee on the Effects of Atomic Radiation. Genetic and somatic effects of ionizing radiation. Official Records of the General Assembly, 41st Session, Suppl 16(A/41/16). New York: United Nations, 1986 (Sales No. E.86.IX.9).
- (42) UPTON AC. Radiobiological effects of low doses: Implications for radiological protection. *Radiat Res* 1977; 71:51-74.
- (43) MOOLGAVKAR SH, VENZON DJ. Confidence regions for case-control and survival studies with general relative risk functions. In: Moolgavkar SH, Prentice RL, eds. *Modern statistical methods in chronic disease epidemiology*. New York: Wiley, 1986: 104-120.
- (44) LAND CE, BOICE JD JR, SHORE RE, et al. Breast cancer risk from low-dose exposures to ionizing radiation: Results of parallel analysis of three exposed populations of women. *JNCI* 1980; 65:353-376.
- (45) BOICE JD JR, LAND CE, SHORE RE, et al. Risk of breast cancer following low-dose radiation exposure. *Radiology* 1979; 131:589-597.
- (46) PRESTON DL, KATO H, KOPECKY KJ, et al. Studies of the mortality of A-bomb survivors. 8. Cancer mortality, 1950-1982. *Radiat Res* 1987; 111:151-178.
- (47) MOLE RH. Ionizing radiation as a carcinogen: Practical questions and academic pursuits. *Br J Radiol* 1975; 48:157-169.
- (48) SMITH PG. Radiation. In: Vessey MP, Gray M, eds. *Cancer risks and prevention*. Oxford: Oxford Univ Press, 1985:119-148.
- (49) —. Leukemia and other cancers following radiation treatment of pelvic disease. *Cancer* 1977; 39:1901-1905.
- (50) BOICE JD JR, KLEINERMAN RA. Meeting Highlights: Radiation studies of women treated for benign gynecologic disease. *JNCI* 1986; 76:549-551.
- (51) GREENE MH, BOICE JD JR, GREER BE, et al. Acute nonlymphocytic leukemia after therapy with alkylating agents for ovarian cancer. A study of five randomized clinical trials. *N Engl J Med* 1982; 307:1416-1421.
- (52) MOLE RH. Dose-response relationships. In: Boice JD Jr, Fraumeni JF Jr, eds. *Radiation carcinogenesis: Epidemiology and biological significance*. New York: Raven Press, 1984:403-420.
- (53) MOLE RH, PAPWORTH DG, CORP MJ. The dose-response for X-ray induction of myeloid leukemia in male CBA/H mice. *Br J Cancer* 1983; 47:285-291.
- (54) MAJOR IR, MOLE RH. Myeloid leukemia in X-ray irradiated CBA mice. *Nature* 1978; 272:455-456.
- (55) HELLMAN S, MOLONEY WC, MEISSNER WA. Paradoxical effect of radiation on tumor incidence in the rat: Implications for radiation therapy. *Cancer Res* 1982; 42:433-436.
- (56) MOLE RH, MAJOR IR. Myeloid leukaemia frequency after protracted exposure to ionizing radiation: Experimental confirmation of the flat dose-response found in ankylosing spondylitis after a single treatment course with X-rays. *Leuk Res* 1983; 7:295-300.
- (57) UPTON AC, RANDOLPH ML, CONKLIN JW, et al. Late effects of fast neutrons and gamma-rays in mice as influenced by the dose rate of irradiation: Induction of neoplasia. *Radiat Res* 1970; 41:467-491.
- (58) ELKIND MM, HAN A, HILL CK. Error-free and error-prone repair in radiation-induced neoplastic cell transformation. In: Boice JD Jr, Fraumeni JF Jr, eds. *Radiation carcinogenesis: Epidemiology and biological significance*. New York: Raven Press, 1984:303-318.
- (59) ELKIND MM, HAN A, HILL CK, et al. Repair mechanisms in radiation-induced cell transformation. In: Broerse JJ, Barendsen GW, Kal HB, et al., eds. *Radiation research. Proceedings of the seventh international congress of radiation research*. Amsterdam: Nijhoff, 1983:33-42.
- (60) LEHNERT S, RYBKA WB, SUISSA S, et al. Radiation response of haematopoietic cell lines of human origin. *Int J Radiat Biol* 1986; 49:423-431.
- (61) COURT BROWN WM, DOLL R. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Br Med J* 1965; 2:1327-1332.
- (62) LAND CE. Estimating cancer risks from low doses of ionizing radiation. *Science* 1980; 209:1197-1203.
- (63) PRESTON DL, PIERCE DA. The effect of changes in dosimetry on cancer mortality risk estimates in the atomic bomb survivors. Hiroshima: Radiation Effects Research Foundation, 1987 (RERF TR 9-87).
- (64) KATO H, SCHULL WJ. Studies of the mortality of A-bomb survivors. 7. Mortality, 1950-1978. Part I. Cancer mortality. *Radiat Res* 1982; 90:395-432.
- (65) TUCKER MA, MEADOWS AT, BOICE JD JR, et al. Leukemia after therapy with alkylating agents for childhood cancer. *JNCI* 1987; 78:459-464.
- (66) National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiations. The effects on populations of exposure to low levels of ionizing radiation. Washing-

ton, DC: Natl Acad Press, 1972:1-217.
 (67) RADFORD EP, DOLL R, SMITH PG. Mortality among patients with ankylosing spondylitis not given x-ray therapy. N Engl J Med 1977; 297:572-576.
 (68) MOLE RH. Radiation-induced acute myeloid leukemia in the

mouse: Experimental observations in vivo with implications for hypotheses about the basis of carcinogenesis. Leuk Res 1986; 7:859-865.
 (69) ELLIS RE. The distribution of active bone marrow in the adult. Phys Med Biol 1961; 5:255-258.

APPENDIX

APPENDIX TABLE 1.— *Participating hospitals and responsible investigators*

Location	Participating hospital	Responsible investigators
Austria, Vienna	University Women's Clinics	H. Kucera
England		
London	London School of Hygiene and Tropical Medicine	P. Fraser, M. P. Coleman, P. G. Smith
Manchester	Christie Hospital and Holt Radium Institute	M. Palmer, A. Crutcher-Pugh, G. Williams
Federal Republic of Germany		
Göttingen	University Women's Clinic	R. Frischkorn, I. Freund
Hamburg	University Women's Clinic	K. Thomsen
Heidelberg	University Women's Clinic	D. von Fournier, U. Schiller
Munich	University Women's Clinic	H. Lochmüller, M. Brach, H. Brach
France, Villejuif	Institute Gustave-Roussy	M. H. Pejovic
Italy		
Bologna	Curie Therapy Unit	F. Volterani
Milan	Ospedale Sant'Orsola	U. Montaguti
Norway, Oslo	National Institute for the Study and Treatment of Tumors	P. Pisani, F. Berrino
Puerto Rico, San Juan	Norwegian Radium Hospital	K. E. Kjørstad
Sweden, Stockholm	I. Gonzalez Martinez Oncologic Hospital	A. Bosch
	Radiumhemmet, Karolinska Hospital	F. Pettersson, E. Björkholm, M. Lundell
United States		
Baltimore	University of Maryland Hospital	R. Scott, T. Pempree
Boston	Massachusetts General Hospital	M. D. Schulz
Buffalo	Roswell Park Memorial Institute	J. Barlow, S. Piver, D. Cookfair
Houston	M. D. Anderson Hospital and Tumor Institute	R. J. Freedman, L. J. Peters, A. Hamburger, V. Guinee, G. Everett
New Orleans	Department of Surgery, Charity Hospital of Louisiana	E. T. Kremetz
Norfolk	Southwood Community Hospital ^a	L. M. Parker, M. D. Schulz

^aFormerly Pondville Hospital.

APPENDIX TABLE 2.— *Participating cancer registries and their responsible investigators*

Location	Participating cancer registry	Responsible investigators
Canada	Alberta Cancer Registry	M. Koch
	Cancer Control Agency of British Columbia	T. G. Hislop
	Manitoba Cancer Treatment and Research Foundation	N. W. Choi
	National Cancer Institute of Canada	A. B. Miller
	New Brunswick Provincial Tumor Registry	D. Robb
	Ontario Cancer Treatment and Research Foundation	E. A. Clarke, R. F. Spengler, J. Price
	Saskatchewan Cancer Foundation	D. Robson
Denmark	Danish Cancer Registry	H. H. Storm, O. M. Jensen
England	Birmingham and West Midlands Cancer Registry	P. Prior
	Thames Cancer Registry	C. M. J. Bell
Finland	Finnish Cancer Registry	M. Hakama, T. Hakulinen, A. Rimpela
Iceland	Icelandic Cancer Registry	K. Sigurdsson, H. Tulinius
Norway	Norwegian Cancer Registry	A. Andersen, K. Magnus, F. Langmark, J. E. Skjerven
Sweden	Swedish Cancer Registry	B. Malke, F. Pettersson
United States	California Department of Health Services	D. Austin, K. Bragg
	Charity Hospital Tumor Registry	J. Rodriguez
	Connecticut Tumor Registry	J. T. Flannery
	Iowa Cancer Registry	H. B. Latourette, K. McKeen
Yugoslavia	Slovenia Cancer Registry	V. Pompe-Kirn, P. Cevc, M. Sok