Reprinted from JAMA® The Journal of the American Medical Association
March 13, 1991, Volume 265
Copyright 1991, American Medical Association

Topics in Radiology

Ronald G. Evens, MD, *Section Editor*

Diagnostic X-ray Procedures and Risk of Leukemia, Lymphoma, and Multiple Myeloma

John D. Boice, Jr, ScD; Michele M. Morin, MS; Andrew G. Glass, MD; Gary D. Friedman, MD; Marilyn Stovall, MS; Robert N. Hoover, ScD, MD; Joseph F. Fraumeni, Jr, MD

Exposure to diagnostic x-rays and the risk of leukemia, non-Hodgkin's lymphoma (NHL), and multiple myeloma were studied within two prepaid health plans. Adult patients with leukemia (n = 565), NHL (n = 318), and multiple myeloma (n = 208) were matched to controls (n = 1390), and over 25000 x-ray procedures were abstracted from medical records. Dose response was evaluated by assigning each x-ray procedure a score based on estimated bone marrow dose. X-ray exposure was not associated with chronic lymphocytic leukemia, one of the few malignant conditions never linked to radiation (relative risk [RR], 0.66). For all other forms of leukemia combined (n = 358), there was a slight elevation in risk (RR, 1.17) but no evidence of a dose-response relationship when x-ray procedures near the time of diagnosis were excluded. Similarly, patients with NHL were exposed to diagnostic x-ray procedures more often than controls (RR, 1.32), but the RR fell to 0.99 when the exposure to diagnostic x-ray procedures within 2 years of diagnosis was ignored. For multiple myeloma, overall risk was not significantly high (RR, 1.14), but there was consistent evidence of increasing risk with increasing numbers of diagnostic x-ray procedures. These data suggest that persons with leukemia and NHL undergo x-ray procedures frequently just prior to diagnosis for conditions related to the development or natural history of their disease. There was little evidence that diagnostic x-ray procedures were causally associated with leukemia or NHL. The risk for multiple myeloma, however, was increased among those patients who were frequently exposed to x-rays.

(*JAMA*. 1991;265:1290-1294)

EACH YEAR about seven of every 10 Americans are examined radiologically[1] and it is not surprising that the possible danger associated with such exposures arouses intense interest, as well as controversy, in both public and scientific forums.[2] Estimates of the total cancer burden attributable to medical radiology have clustered around 1% for leukemia[3] and perhaps 1% to 2% for all other cancers.[4,5] Recently, however, a National Academy of Sciences' committee reported that estimates of lifetime cancer risk following relatively low doses of radiation may be as much as four times larger than previously thought.[6]

Several case-control studies of leukemia and multiple myeloma have evaluated diagnostic x-ray procedures,[7-13] but results are inconsistent, partly because the magnitude of the possible effect from such low doses of radiation is so small compared with the natural occurrence of cancer.[14] Other limitations include the potential for recall bias in interview surveys, incomplete verification of the actual number of diagnostic x-ray procedures, limited dosimetry, and small study sizes such that only very high levels of risk could be detected.[15,16] Further, it is conceivable that x-ray procedures performed shortly before a diagnosis of leukemia might be prompted by symptoms connected with preclinical disease.[17] In this circumstance, x-ray exposure might not be a leukemogenic factor, but rather a marker of conditions portending the development of disease. To address these methodologic issues and potential biases, we conducted a case-control study within two prepaid health plans.

METHODS

Population

Adult cases of leukemia, non-Hodgkin's lymphoma (NHL), and multiple myeloma were selected from computerized files of two Kaiser Permanente prepaid health plans. Diagnoses were available between 1959 and 1979 in Portland, Ore, and between 1956 and 1982 in northern California. Children who were younger than 15 years were not included, nor were persons who were treated previously with either radiotherapy or chemotherapy. The histologic diagnoses recorded in the medical records were assumed to be accurate. Controls were matched to cases within the same plan on the basis of sex, age, number of years as a member in the plan, and calendar year in which membership began. Two controls per case were selected in Portland, and one control per case in northern California. In northern California, some cases and controls from previous studies of leukemia and multiple myeloma were included in the present investigation but with more detailed information on diagnostic x-ray procedures.[11,18] Appropriately matched controls could not be found for

From the Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Md (Drs Boice, Hoover, and Fraumeni and Ms Morin); the Kaiser Permanente Medical Care Program, Portland, Ore (Dr Glass); the Kaiser Permanente Medical Care Program, Oakland, Calif (Dr Friedman), and the M. D. Anderson Cancer Center, Houston, Tex (Ms Stovall).

Reprint requests to Radiation Epidemiology Branch, National Cancer Institute, 6130 Executive Blvd, Executive Plaza North, Room 408, Bethesda, MD 20852 (Dr Boice).

67 cases of leukemia, six cases of NHL, and 35 cases of multiple myeloma. Altogether, 565 patients with leukemia, 318 patients with NHL, 208 patients with multiple myeloma, and 1390 controls were studied (Table 1).

More than 60% of the population studied were men, the median age at entry into the Kaiser Permanente plans was approximately 45 years of age, more than 33% of the participants were members for more than 15 years, and 28% began their membership prior to 1955 (Table 2). Higher cumulative x-ray exposure was associated with increased age, longer length of membership, and being female.

Table 1.—Distribution of Cases and Controls by Disease and Number of X-ray Procedures

Disease	No. of Subjects	Exposed Subjects, %	No. of X-ray Procedures	Average No. of X-ray Procedures	High-Exposure X-ray Procedures, %*†
Chronic lymphatic leukemia					
Cases	207	86.5	2158	12.1	14.7
Controls	238	90.8	2332	10.8	12.1
Other leukemia‡					
Cases	358	81.3	3528	12.1	9.7
Controls	441	81.2	3889	10.9	12.6
Non-Hodgkin's lymphoma§					
Cases	318	92.8	3309	11.2	16.8
Controls	449	91.3	4130	10.1	15.6
Multiple myeloma					
Cases	208	96.2	3097	15.5	8.5
Controls	262	95.8	2978	11.9	8.4

*Among the exposed subjects only.

†Percentage of total x-ray procedures that were fluoroscopes, multifilm, or other procedures classified as "high-exposure" relative to routine x-ray procedures, such as chest examinations.

‡Includes 186 cases of acute myelogenous leukemia, 71 cases of acute lymphatic leukemia, 73 cases of chronic myelogenous leukemia, 14 cases of monocytic leukemia, and 14 other or unclassified cases.

§Includes 120 cases of reticulum cell sarcoma, 191 cases of lymphosarcoma, and seven other cases.

Table 2.–Characteristics of Cases and Matched Controls

Characteristic	Cases, % (n = 1091)	Controls, % (n = 1390)	Average No. of X-ray Procedures*	High-Exposure X-ray Procedures, %*†
Sex				
Male	60.8	60.6	10.9	13.1
Female	39.2	39.4	12.6	11.4
Age at entry into health plan				
<30 y	15.9	15.0	6.0	9.3
30-49 y	40.6	39.6	12.4	11.3
≥50 y	43.5	45.4	12.1	13.7
Calendar year of entry into health plan				
Before 1955	28.2	27.0	17.5	12.8
1955-1964	30.5	31.5	11.3	12.5
1965 and after	41.3	41.5	7.0	11.4
No. of years as health plan member				
<5	23.1	23.7	4.1	13.2
5-14	42.6	43.5	9.1	12.4
≥15	34.3	32.8	18.4	12.3
Prepaid health plan				
Northern California	71.3	56.0	11.7	12.5
Portland, Ore	28.7	44.0	11.4	12.2

*Among the exposed cases and controls combined.

†Percentage of total x-ray procedures that were fluoroscopes, multifilm, or other procedures classified as "high-exposure" relative to routine x-ray procedures, such as chest examinations.

Dosimetry

Information for more than 25000 diagnostic x-ray procedures was abstracted directly from medical records and then classified.[19] Each diagnostic x-ray procedure was assigned a probable dose to the active bone marrow (averaged over the whole body), based on an extensive literature review of bone marrow doses associated with diagnostic x-ray procedures over a period of almost 30 years.[20-28] No new measurements were performed.

For each individual, the cumulative bone marrow dose was estimated by summing the dose per examination for all diagnostic x-ray procedures. In general, less than five diagnostic x-ray procedures contributed between 0.00001 to 0.03 Gy; five to 14 diagnostic x-ray procedures, 0.0001 to 0.05 Gy; and 15 or more diagnostic x-ray procedures, 0.001 to 0.23 Gy. The variation in these numbers is due to the different bone marrow doses associated with different diagnostic x-ray procedures. For example, a chest roentgenogram would contribute about 0.0001 Gy to the cumulative dose, whereas an upper gastrointestinal tract procedure might contribute 0.006 Gy.

Statistical Procedures

Conditional logistic regression methods were used to estimate relative risk (RR) and 95% confidence intervals, taking into account the varying number of controls per case.[29] Subjects were distributed over five categories of cumulative bone marrow dose, and exposure scores of 0 through 4 were assigned based on nominal dose categories of 0.01 Gy. Because of the inherent limitations in these dose estimates, they should not be taken literally. The RRs for each category, relative to the nonexposed study population, were computed. Tests for trend were based on the significance levels for the linear slope parameter in the matched regression with the covariate taken as the exposure scores.

The diagnostic x-ray procedures taken near the time of case diagnosis were evaluated by "lagging" or excluding exposures. With a 2-year lag, for example, the cumulative x-ray exposure for a patient who developed leukemia at age 50 years would be calculated only up to age 48 years. The RRs and dose-response trends were recomputed after excluding the diagnostic x-ray procedures that were performed during various intervals prior to diagnosis. Two-year minimal latent periods are considered appropriate for leukemia and latent periods of 5 to 10 years for other cancers.[30]

RESULTS

More than half (51.6%) of the 25421 diagnostic x-ray procedures recorded in the medical records were roentgenograms of the chest (Table 3). The average number of diagnostic x-ray procedures received by each exposed subject was 11.6; about 12% of all exposures were relatively high-dose fluoroscopic or multifilm procedures. No record of a diagnostic x-ray procedure was noted for 11.6% of the cases and 11.2% of the controls. About 9% of the population was examined radiologically over 25 times. One individual underwent 142 x-ray procedures.

Table 4 shows that the 207 cases of chronic lymphocytic leukemia (CLL)

were exposed to diagnostic radiation less frequently than their controls (RR, 0.66). For the other leukemias, a nonsignificant 17% excess risk was observed (RR, 1.17). Small nonsignificant associations with diagnostic x-ray procedures were also seen for NHL (RR, 1.32) and for multiple myeloma (RR, 1.14).

Dose-response and lagging analyses were carried out to clarify the possible causal nature of these associations. For CLL, lagging exposures had little effect on the RR estimate until a 5-year lag interval, when the deficit became significant (RR, 0.51). For the other leukemias combined, pattern of risk appeared to flatten over categories of exposure when exposures just prior to diagnosis were excluded.

Similarly, the risk for NHL dropped to normal levels (RR, 0.99) when x-ray procedures performed within 2 years of diagnosis were excluded. With the elimination of these recent diagnostic x-ray procedures, a dose-response trend of borderline significance was no longer evident.

For multiple myeloma, the exclusion of x-ray procedures performed within 2 years of diagnosis increased the RR slightly, from 1.14 to 1.33. However, in contrast to the results for leukemia and NHL, the dose-response trend did not change appreciably. All of the trends approached statistical significance, mainly because of the high RR seen among those patients in the highest x-ray exposure category (mean number of examinations, 39). For the 135 cases who contributed to an analysis with a 10-year lag interval, the RR equaled 1.50, and there was continued evidence of a dose-response relationship (trend $P = .05$). The association with x-ray procedures was evident only in northern California and only in women (RR, 3.8) and not men (RR, 0.7).

Table 3.–Distribution of Specific Diagnostic X-ray Procedures for All Study Subjects, Both Cases and Controls

X-ray Procedures Diagnostic Code*	No. (%)†
Chest (71000-71199)	13 120 (51.6)
Gastrointestinal tract (74210-74399)	3029 (11.9)
Upper gastrointestinal examination (74242-74245)	1337 (5.3)
Lower gastrointestinal examination (74270-74280)	985 (3.9)
Spine and pelvis (72010-72999)	2585 (10.2)
Lower extremities (73500-73999)	1827 (7.2)
Upper extremities (73000-73499)	1587 (6.2)
Head and neck (70002-70999)	949 (3.7)
Urinary tract (74400-74470)	926 (3.6)
Abdomen (74000-74020)	686 (2.7)
Vascular system (75500-75999)	123 (0.5)
Other and unknown	589 (2.3)
Total	25 421 99.9‡

*California Standard Nomenclature code.[19]
†We have excluded 1649 x-ray procedures because their contribution to bone marrow dose was less than 0.00001 Gy. Practically all involved the hands or feet.
‡Difference from 100% due to rounding.

COMMENT

It is no longer disputed that ionizing radiation is a cause of cancer. Considerable controversy exists, however, over the magnitude of the risk from low-level exposures delivered over many years, such as experienced in the healing arts. Despite an extensive evaluation of the radiologic experience of 565 cases of leukemia and 318 cases of NHL within two large health maintenance organizations, we were not able to demonstrate convincingly an association with diagnostic x-ray procedures. On the other hand, very large numbers of x-ray procedures appeared to increase the risk of multiple myeloma after a relatively long latency period.

Leukemia

There was no evidence that diagnostic x-ray procedures increased the risk of developing CLL, a tumor that has never been linked with exposure to ionizing radiation.[31-33] Interestingly, excluding exposures that were performed within 5 years of diagnosis resulted in a significant negative association with use of diagnostic x-ray procedures. The reasons for this "protective effect" are not entirely clear, and might be due simply to chance or to a peculiar ascertainment bias discussed below. Bias in the recording of diagnostic x-ray procedures seems unlikely, because abstractors were not aware whether a case or control record was being abstracted.

For the 358 cases of leukemia other than CLL, risk among the most heavily

Table 4.–Matched Relative Risk (RR) of Diagnostic X-ray Procedures and Leukemia, Non-Hodgkin's Lymphoma, and Myeloma by Exposure Score and Various Exposure-Lag Categories*

Exposure-Lag Interval*	No. of Cases	RR†	95% Confidence Interval	Exposure Score (Mean No. of X-ray Procedures‡) 0 (0)	1 (6)	2 (15)	3 (21)	4 (35)	P
Chronic lymphocytic leukemia (CLL)									
3 mo	207	0.66	0.4-1.2	1.0	0.6	0.6	0.5	0.9	.95
2 y	194	0.56	0.3-1.1	1.0	0.5	0.6	0.5	0.7	.85
4 y	173	0.67	0.4-1.3	1.0	0.6	0.8	1.0	0.8	.88
5 y	163	0.51§	0.3-0.9	1.0	0.5§	0.6	0.7	0.8	.86
Non-CLLs									
3 mo	358	1.17	0.8-1.8	1.0	1.2	1.2	2.3§	1.2	.45
2 y	326	1.42	0.9-2.2	1.0	1.4	1.7	1.8	1.4	.51
4 y	264	1.13	0.7-1.8	1.0	1.1	1.2	1.1	0.7	.38
5 y	246	1.04	0.6-1.8	1.0	1.0	1.1	1.0	0.6	.22
Non-Hodgkin's lymphoma									
3 mo	318	1.32	0.7-2.3	1.0	1.3	1.3	2.0	1.8	.06
2 y	302	0.99	0.6-1.6	1.0	1.0	0.9	1.6	1.2	.32
4 y	266	1.24	0.8-2.0	1.0	1.2	1.2	1.7	1.3	.77
5 y	251	1.06	0.7-1.7	1.0	1.1	1.0	1.1	1.1	.89
Multiple myeloma									
3 mo	208	1.14	0.4-3.1	1.0	1.1	1.1	0.9	2.8	.06
2 y	198	1.33	0.6-3.0	1.0	1.3	1.5	1.3	3.9§	.03
4 y	186	1.07	0.6-2.0	1.0	1.1	1.0	1.0	4.5§	.07
5 y	175	1.21	0.6-2.4	1.0	1.2	1.3	1.9	3.6	.08

*The interval prior to the diagnosis of each malignant disease for which the x-ray exposure is ignored.
†RR for any x-ray exposure vs none.
‡Mean number of x-ray procedures is presented for all cases and controls combined and differed slightly among the individual disease groupings.
§ $P < .05$.

x-ray-exposed cases dropped to near normal levels when recent x-ray procedures were excluded from the analyses. This implies that many diagnostic x-ray procedures were performed for conditions, such as an increased susceptibility to infections, that occurred during the precursor or early stages of leukemia. There is a minimum time required for a cancer to develop after radiation exposure. For leukemia this minimum latency period is about 2 years, and any x-ray procedures that occurred within this interval are unlikely to be related causally to the disease. Exposures that occur within 2 to 5 years prior to diagnosis could, conceivably, affect disease occurrence. However, more than half of any radiation-induced leukemias would be expected to occur 5 years or longer after exposure, and some as long as 30 years later.[6] Excluding x-ray procedures performed 4 years prior to diagnosis revealed a flat dose-response relationship and no increased risk among subjects with the greatest x-ray exposure, and thus provided little support for an association between diagnostic x-ray procedures and leukemia, which was suggested in several previous series.[8,9,13] One study reported a significant association between diagnostic x-ray procedures and chronic myeloid and monocytic leukemias based on personal interviews of 136 cases and 136 neighborhood controls.[13] In our series there was no overall association between diagnostic x-ray procedures and chronic myeloid and monocytic leukemias (RR, 0.93; 95% confidence interval, 0.3 to 3.3). These analyses, however, are based on only 87 cases of chronic myeloid and monocytic leukemias.

Studies of pioneering radiologists and medical x-ray technologists in the United States,[34,35] England,[36] and China[37] have shown that leukemia can result from frequent exposure to low doses of radiation over many years, although the cumulative doses were likely quite large and between 1 and 8 Gy. Among patient populations who were exposed to diagnostic radiation, no excess leukemia has been reported among patients with tuberculosis who were subjected to repeated chest fluoroscopies,[38] women who were exposed to frequent spinal diagnostic x-rays to monitor scoliosis during adolescence,[39] or children who were exposed to lengthy fluoroscopes during heart catheterization procedures.[40] It is generally found in animal experiments that protracting x-ray exposures over time usually results in much lower leukemia risks than from single, brief exposures of the same total dose, supposedly related in part to a greater opportunity for cellular mechanisms to repair radiation damage.[41] Further, the prevailing dose-response model for leukemia is linear-quadratic in dose, which means that the risk per unit dose is lower at low doses than at higher doses.[6]

NHL

The 318 cases of NHL were exposed to diagnostic x-ray procedures more often than controls, but no relationship was seen when recent exposures were excluded. This pattern also suggests that the diagnostic x-ray procedures were administered for conditions that arose during the early phases of lymphoma development. This interpretation is supported by the available epidemiologic evidence that suggests that NHL may arise only following very high-dose, possibly near-lethal, exposures.[31] Patients who were given radiotherapy for spondylitis[12] and cervical cancer,[43] for example, appear at increased risk. Early studies of atomic bomb survivors suggested an excess of NHL,[44] but recent surveys have not been confirmatory.[32] Except for an American survey,[35] studies of radiologists and x-ray technicians have not reported elevated rates of NHL.[36,37]

Myeloma

Overall, the 208 cases of multiple myeloma did not receive significantly more x-ray exposure than controls (RR, 1.14); however, there was consistent evidence for a dose-response trend regardless of the lagging interval. The most frequently exposed were at highest risk, reaching fourfold. The causal nature of the association between ionizing radiation and myeloma has been questioned.[31,45] Although some studies are positive,[32,46-48] others are not.[38,43,49,50] A recent case-control study of 399 cases of myeloma and 399 controls in England found no association with diagnostic x-ray procedures,[12] nor did a previous medical record review study of 327 cases and 327 controls.[11]

Methodologic Issues

Several strengths and weaknesses of our study should be considered when interpreting the results. Because all information relating to diagnostic x-ray exposure was abstracted from the medical records of clinics and hospitals within prepaid health plans, the possibility of recall bias was eliminated. The absence of an x-ray exposure association with CLL, a malignant condition not known to be caused by radiation, suggests that the abstraction and dosimetry procedures were performed without serious bias. Surveillance bias also seems unlikely, because cases and controls were at equal risk for having their diagnostic x-ray procedures recorded and they had equal opportunity for being diagnosed with a hematologic malignant condition. Our survey is one of the largest so far to evaluate the risk of adult leukemia associated with diagnostic x-ray procedures, thus minimizing the role of chance.

Ascertainment bias, however, might operate in several ways. If a patient was being examined for an unrelated condition, there would be an opportunity to diagnose one of the index malignant conditions being studied. The x-ray exposure might be excessive, then, just prior to the incidental diagnosis of an index malignant condition, simply because of the workup for an unrelated problem. However, the influence of unrelated conditions might be different for diseases such as CLL, which can remain indolent and undiagnosed for many years. Among persons with CLL, the workup for an unrelated condition might include blood tests leading to the diagnosis of CLL. Among controls, such a workup might lead only to increased diagnostic x-ray procedures. Conceivably, such a peculiar "ascertainment bias" may explain the inverse relationship observed between diagnostic x-ray procedures and CLL.

Since no actual radiation dosimetry was performed, these data can only be used to estimate radiation risk in a semiquantitative manner. Although counts of x-ray exposure were accurate, the conversion of these counts to bone marrow doses was based on assumptions of average values from the literature. In addition, diagnostic x-ray examinations that were repeated because of inadequate initial radiographs would not have been recorded, and exposure times for fluoroscopic machines could vary appreciably, from several minutes to over an hour. Exposures also came from a great many machines, and there is a wide range of doses possible for a given examination.[51] Accordingly, analyses were conducted using exposure scores and numbers of x-ray procedures to avoid the misrepresentation that "real" doses were determined. Risk estimates per 0.01 Gy could be in error by a very large factor. On the other hand, differential biases in assigning scores to cases and controls were unlikely, and subjects could be separated into relatively broad categories of x-ray exposure. That is, subjects who were exposed to diagnostic x-ray procedures more than 40 times likely received more dose to bone marrow than subjects who were exposed to x-ray procedures only five times. Finally, coverage under the health plans spanned 5 to 25 years, so

that an assessment of an individual's lifetime exposure to x-rays was not possible.

In summary, our findings are, for the most part, reassuring, and confirm that diagnostic x-ray procedures are unlikely to be a major cause of leukemia, lymphoma, or myeloma in our society. Nonetheless, the potential hazards from radiologic examinations should be weighed against the medical benefits.[1,52] Nearly 90% of the total collective dose to the population from man-made sources comes from diagnostic x-ray procedures, but about one in every five x-ray procedures may be unnecessary.[53] Thus, the judicious use of radiologic examinations and the elimination of nonproductive procedures should always be encouraged.[30,53-55]

This research was partially supported by contracts N01-CP0-1047, N01-CP0-1054, N0l-CPl-1009, N01-CP1-1037, N01-CP3-1035, and N0l-CP6-l006 from the National Cancer Institute, Bethesda, Md.

We are indebted to the staffs of the Kaiser Permanente prepaid health plans and hospitals in California and Oregon whose cooperation made this study possible; to Brenda Rush and Julie Truby of Kaiser Permanente, Portland, and to Bill Frank, Shreela Goel, Merril Jackson, Dorothy Sawyer, Fran Singleton, Joan Thomas, Beverly Whitmarsh, and Betty Wang of Kaiser Permanente, Oakland, for data abstraction and preparation; to Rita Weathers and Susan A. Smith of the M. D. Anderson Cancer Center for data management associated with dosimetry; to Cathy Drzyzgula and Joseph Barker of Information Management Services Inc (Rockville, Md), Charles Eastlack of Westat Inc (Rockville, Md), and Robert Weinstock, formerly of Operations Research Inc (Rockville, Md), for computing support; and to Maria Klebanoff for manuscript typing.

References

1. National Council on Radiation Protection and Measurements. *Exposure of the US Population From Diagnostic Medical Radiation.* Bethesda, Md: National Council on Radiation Protection and Measurements; 1989. Report 100.
2. Boice JD Jr. The danger of X-rays–real or apparent? *N Engl J Med.* 1986;315:828-830.
3. Evans JS, Wennberg J E, McNeil BJ. The influence of diagnostic radiography on the incidence of breast cancer and leukemia. *N Engl J Med.* 1986;315:810-815.
4. Kohn HI, Fry RJM. Radiation carcinogenesis. *N Engl J Med.* 1984;310:504-511.
5. Jablon S, Bailar JC III. The contribution of ionizing radiation to cancer mortality in the United States. *Prev Med.* 1980;9:219-226.
6. National Academy of Sciences, National Research Council. *Health Effects of Exposure to Low Levels of Ionizing Radiation: The Committee on the Biological Effects of Ionizing Radiations* (BEIR V). Washington, DC: National Academy Press; 1990.
7. Stewart A, Penny backer W, Barber R. Adult leukaemias: a retrospective survey. *BMJ.* 1962; 2:882-890.
8. Gunz F W, Atkinson HR. Medical radiations and leukaemias: a retrospective survey. *BMJ.* 1964; 1:389-393.
9. Gibson R, Graham S, Lilienfeld A, Schuman L, Dowd JE, Levin ML. Irradiation in the epidemiology of leukemia among adults. *J Natl Cancer Inst.* 1972;48:301-311.
10. Linos A, Gray JE, Orvis AL, Kyle RA, O'Fallon WM, Kurland, LT. Low-dose radiation and leukemia. *N Engl J Med.* 1980;302:1101-1105.
11. Friedman GD, Multiple myeloma: relation to propoxyphene and other drugs, radiation and occupation. *Int J Epidemiol.* 1986;15:424-426.
12. Cuzick J, DeStavola B. Multiple myeloma–a case-control study. *Br J Cancer.* 1988;57:516-520.
13. Preston-Martin S, Thomas DC, Yu MC, Henderson BE. Diagnostic radiography as a risk factor for chronic myeloid and monocytic leukaemia (CML). *Br J Cancer.* 1989;59:639-644.
11. Land CE. Estimating cancer risks from low doses of ionizing radiation. *Science.* 1980;209:1197-1203.
15. Graham S, Levin ML, Lilienfeld AM, et al. Methodological problems and design of the Tristate Leukemia Survey. *Ann N Y Acad Sci.* 1963; 107:557-569.
16. Boice JD Jr, Land CE. Adult leukemia following diagnostic x-rays? *Am J Public Health.* 1979;69:137-145.
17. Stewart A. The carcinogenic effects of low level radiation: a reappraisal of epidemiologists' methods and observations. *Health Phys.* 1973;24:223-240.
18. Friedman GD. Phenylbutazone, musculoskeletal disease, and leukemia. *J Chronic Dis.* 1982;35:233-243.
19. California Medical Association. *California Standard Nomenclature.* San Francisco, Calif: Sutter Publications; 1979.
20. Kereiakes JG, Rosenstein M. *Handbook of Radiation Doses in Nuclear Medicine and Diagnostic X-ray.* Boca Raton, Fla: CRC Press Inc; 1980.
21. Shleien B, Tucker TT, Johnson DW. The mean active bone marrow dose to the adult population of the United States from diagnostic radiology. *Health Phys.* 1978;34:587-601.
22. Antoku S, Russell WJ. Dose to the active bone marrow, gonads, and skin from roentgenography and fluoroscopy. *Radiology.* 1971;101:669-678.
23. Jankowski J. Organ doses in diagnostic X-ray procedures. *Health Phys.* 1984;46:228-234.
24. Johnson DW, Goetz WA. Patient exposure trends in medical and dental radiography. *Health Phys.* 1986;50:107-116.
25. Recommendations of the International Commission on Radiological Protection. *Protection of the Patient in X-ray Diagnosis.* New York, NY: Pergamon Press Inc; 1970. Publication 16.
26. United Nations Scientific Committee on the Effects of Atomic Radiation. *Report to the General Assembly.* New York, NY: United Nations; 1962; suppl 16 (A/5216). Seventeenth Session.
27. United Nations Scientific Committee on the Effects of Atomic Radiation. *Report to the General Assembly.* New York, NY: United Nations; 1972; suppl 25 (A/8725). Twenty-seventh Session.
28. United Nations Scientific Committee on the Effects of Atomic Radiation. *Report to the General Assembly.* New York, NY: United Nations; 1977; suppl 40 (A/32/40). Thirty-second Session.
29. Lubin JH. A computer program for the analysis of matched case-control studies. *Comput Biomed Res.* 1981;14:138-143.
30. United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources, Effects, and Risks of Ionizing Radiation.* New York, NY: United Nations; 1988, Publication E.88.IX.7.
31. Rall JE, Beebe GW, Heel DC, et al, *Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables.* Washington, DC: US Dept of Health and Human Services; 1985. Publication (NIH) 85-2748.
32. Shimizu Y, Kato H, Schull WJ. Studies of the mortality of A-bomb survivors: 9. Mortality. 1950-1985, Part 2. Cancer mortality based on the recently revised doses (DS86). *Radiat Res.* 1990;121:120-141.
33. Boice JD Jr, Blettner M, Kleinerman RA, et al. Radiation dose and leukemia risk in patients treated for cancer of the cervix. *J Natl Cancer Inst.* 1987;79:1295-1311.
34. Lewis EB. Leukemia, multiple myeloma, and aplastic anemia in American radiologists. *Science.* 1963;142:1492-1494.
35. Matanoski GM, Seltser R, Sartwell PE, Diamond EL, Elliot EA. The current mortality rate of radiologists and other physician specialists: specific causes of death. *Am J Epidemiol.* 1975;101: 199-210.
36. Smith PG, Doll R. Mortality from cancer and all causes among British radiologists. *Br J Radiol.* 1981;54:187-194.
37. Wang J-X, Boice JD Jr, Li B-X, Zhang J-Y, Fraumeni JF Jr. Cancer among medical diagnostic x-ray workers in China. *J Natl Cancer Inst.* 1988:80:344-350.
38. Davis FG, Boice JD, Kelsey JL, Monson RR. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. *Cancer Res.* 1989;49:6130-6136.
39. Hoffman DA, Lonstein JE, Morin MM, Visscher W, Harris BSH III, Boice JD Jr. Breast cancer in women with scoliosis exposed to multiple diagnostic x-rays. *J Natl Cancer Inst.* 1989 81:1307-1312.
40. Spengler RF, Cook DH, Clarke EA, Olley PM, Newman AM. Cancer mortality following cardiac catheterization: a preliminary follow-up study on 4891 irradiated children. *Pediatrics.* 1983;71: 235-239.
41. United Nations Scientific Committee on the Effects of Atomic Radiation. *Genetic and Somatic Effects of Ionizing Radiation.* New York, NY: United Nations; 1986. Publication E.86.IX.9.
42. Darby SC, Doll R, Gill SK, Smith PG. Long-term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. *Br J Cancer.* 1987;35:179-190.
43. Boice JD Jr, Engholm G, Kleinerman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res* 1988;116:3-55.
44. Anderson RE, Ishida K. Malignant lymphoma in survivors of the atomic bomb in Hiroshima. *Ann Intern Med.* 1964;61:853-862.
45. Miller RW, Beebe GW. Leukemia, lymphoma, and multiple myeloma. In: Upton AC, Albert RE, Burns FJ, Shore RE, eds. *Radiation Carcinogenesis.* New York, NY: Elsevier Science Publishing Co Inc; 1986:245-260.
46. Smith PG, Douglas AJ. Mortality of workers at the Sellafield plant of British Nuclear Fuels. *BMJ.* 1986;293:845-854.
47. Gilbert ES, Petersen GR, Buchanan JA. Mortality of workers at the Hanford site: 1945-1981. *Health Phys.* 1989;56:11-25.
48. Cuzick J. Radiation-induced myelomatosis. *N Engl J Med.* 1981;304:204-210.
49. Beral V, Inskip H, Fraser P, Booth M, Coleman D, Rose G. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946-1979. *BMJ.* 1985;291:440-447,
50. Checkoway H, Mathew RM, Shy CM, et al. Radiation, work experience, and cause-specific mortality among workers at an energy research laboratory. *Br J Ind Med.* 1985;42:525-533.
51. Shrimpton PC, Wall BF, Jones DG, et al. Doses to patients from routine diagnostic x-ray examinations in England. *Br J Radiol.* 1986;59: 749-758.
52. Abrams HL. Overutilization of x-rays. *N Engl J Med.* 1979;300:1213-1216.
53. Avoiding unnecessary patient exposure to radiation. *Lancet.* 1990;2:681.
54. Cohen M. Quality assurance as an optimizing procedure in diagnostic radiology. In: *Criteria and Methods for Quality Assurance in Medical Diagnosis.* London, England: British Institute of Radiology; 1985:134-141. Supplement 18.
55. World Health organization. *A Rational Approach to Radiodiagnostic Investigations.* Geneva, Switzerland: World Health Organization; 1983. Publication TRS-689.

Printed and Published in the United States of America