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SPECIAL ARTICLE

RADIATION-INDUCED MYELOMATOSIS

JACK CUZICK, PH.D.

Abstract It is well known that radiation can cause myeloid leukemia. However, no excess of chronic lymphocytic leukemia has been observed. Myelomatosis, like chronic lymphocytic leukemia, is a tumor of B lymphocytes. To determine whether this disease has a radiogenic origin, we surveyed all cohorts of persons exposed to radiation for which data on cancer-related mortality are available.

An excess of myeloma was found in most cohorts. However, a striking deficit was found in two groups irradiated intensely for uterine neoplasms (three cases observed, 10.71 expected; P = 0.012). All other groups combined had a highly significant excess (50 observed, 22.21 expected; P = 2×10^{-7}). The largest relative risk appeared among persons receiving internal doses of a-particles (14 observed, 3.24 expected; P = 2×10^{-5}), but a significant excess (13 observed, 6.33 expected; P = 0.026) was also found in patients receiving only therapeutic or diagnostic γ-rays or x-rays. Most cases occurred 15 to 25 years after exposure. (N Engl J Med. 1981; 304: 204-10.)

THE evidence that radiation causes myeloid leukemia is now overwhelming, and current interest has centered on the shape of the dose-response curve.[1-4] Radiation also produces cancer in many other tissues of the body, although the latency period is usually much longer.[1] Chronic lymphocytic leukemia, however, is one exception; an excess of this disease does not appear to result from exposure to radiation.[1,2,5]

Since chronic lymphocytic leukemia is predominantly a disease of B lymphocytes[6] (the remaining few cases have T-lymphocyte markers[7]), it is of interest to examine the evidence for the radioinduction of other tumors of B lymphocytes, particularly myelomatosis. The case for radiation as a cause of myelomatosis is generally thought to be much weaker than that for radioinduction of myeloid leukemia, and is based on small numbers of myelomas reported incidentally in cohorts in which other cancers (most often leukemia) were of major interest. Although myelomatosis and myeloid leukemia are both cancers that present in the bone marrow, they are very different diseases. Myeloid leukemia affects granulocyte and macrophage precursors, in contrast to the B-cell lineage of the neoplastic plasma cells in myeloma. Radiation-induce leukemia usually becomes evident between two and 15 years after exposure, whereas the scanty data available suggest that any excess in the incidence of myeloma does not begin to appear for at least 10 years after exposure and may continue for 30 years or more. Perhaps because similar mechanisms govern the period between exposure and manifestation in spontaneous cases of these two diseases, their age distributions are different. Spontaneous myeloma tends to occur later in life, and unlike myeloid leukemia, myeloma has an incidence that grows as approximately the fifth or sixth power of age in common with many epithelial tumors.[8,9]

The purpose of this study was to bring together

From the Cancer Epidemiology and Clinical Trials Unit, University of Oxford, 9 Keble Rd.. Oxford OX1 3QG, England, where reprint requests should be addressed.

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in some cases to update) information from as cohorts exposed to radiation as possible, in o obtain a more comprehensive understanding p ential risk. In some instances, expected numbers of myelomas are not directly available, and it was essary to derive them indirectly. This process inably leads to some inaccuracies, but they were bably not large enough to affect the main conclu- To overcome selection bias, I attempted to inde, every radiation-exposed cohort in which a kdown of cancer incidence or cancer-related mor- by site has been published.

Methods

tical Methods

statistical analysis used significance tests for Poisson and bi- ial variables and confidence intervals for risk ratios between ex- d and control populations.[10] In estimates of expected numbers d on national rates. Poisson statistics were used, whereas bi- ial statistics were used for cohorts that had been standardized ally by their own nonexposed control groups. In the latter he expected numbers used for significance testing were com- from the whole cohort under the assumption of no effects of ; thus, the ratio of observed to expected cases is nearer to han is the risk ratio, in which numbers of expected cases were the unexposed population alone. This difference is most in cohorts in which the exposed group was a substantial n of the entire cohort and the risk ratio was effectively dif- m unity.

for a trend with increasing exposure[11] was used to com- from different exposure categories among atomic-bomb . Since it was not possible to assess exposure levels accu- many cohorts, I combined the results from different co- adding individual numbers of observed and expected cases ying Poisson statistics to the result. This method is conser- two counts: the added power gained from ordering mean els is not obtained,[11] and the approximation of binomial- ted variables by Poisson variables in two cohorts in- he computed variance slightly when combined compari- made, and implies that the results are slightly more sig- than the reported P values indicate.[12]

ided significance levels were used throughout the analysis.

Under Review

rongest evidence linking radiation with myeloma appears ecent report of Ichimaru et al.[13] on the atomic-bomb survi- Other sources considered include workers in the nuclear in- , radium-dial painters, uranium miners and millers, radiolo- patients given Thorotrast (thorium oxide), and patients given e radium therapeutically for ankylosing spondylitis, tuber- gynecologic disorders, or other conditions

Results

Bomb Survivors

maru et al.[13] reported a total of 22 cases of mye- n persons exposed to the atomic bomb who re- n Nagasaki or Hiroshima on October 10, 1950. the hypothesis of no radiation-induced risk, the d numbers of myelomas adjusted for sex, age, in three exposure groups are given in Table 1 th risk ratios comparing the group exposed to less with the groups with more exposure. The among persons exposed to 100 rads or more ificantly (P = 0.028) in excess of the expected number of 1.59. These cases occurred 14, 18, 20, 23, and 27 years after exposure. A nonsignificant excess was also seen in the group exposed to 1 to 99 rads (P = 0.55). Full use of these data may be obtained from an analysis of trend; this method showed a highly significant increasing risk with dose level (P = 0.006). The relative amounts of y-ray and fission neutrons differed between the two Japanese cities, and Ichimaru's analysis suggested that the excess of myeloma was associated more closely with γ-irradiation. Thus, strong evidence was obtained for the radiogenesis of myeloma by high levels of certain types of radiation. However, the data are equivocal in the important 10-to-50-rad range, and because of the neutron flux, these data may not be directly applicable to the more common industrial and clinical exposures to y-irradiation and x-rays.

Table 1. Cases of Myeloma in Atomic-Bomb Survivors.*

Variable	Radiation Exposure		
	<1 rad	1–99 rads	>100 rads
No. of observed cases	7	10	5
No. of expected cases †	10.45	9.95	1.59
Risk ratio ‡	1.0	1.5	4.1

*P = 0.028 for comparison between groups receiving <1 rad and >100 rads. P = 0.55 (not significant) for comparison between groups receiving <1 rad and 1-99 rads. Z = 2.75 and P = 0.006 (normal approximation) lor analysis of trend. Data are from Ichimaru et al.[13]

†Expected numbers of cases were calculated under the assumption that the 22 observed cases were distributed among the population without regard to exposure.

‡Risk ratios assumed unity risk in the group exposed to <1 rad.

Occupational Exposures to Radiation

Nuclear Workers

Reports of cancer-related mortality among workers in nuclear processing plants at Hanford, Washington, and Windscale, England, have shown an excess of myeloma on the basis of a small number of cases. Eleven cases have been reported among all employees at Hanford. The original method of analysis used by Mancuso et al.[14] is open to many valid criticisms, however, and their results should be discounted. A more appropriate, though indirect, analysis by Anderson[15] arrived at an expected number of 8.1 myelomas among all employees. More recently, Gilbert and Marks[16] further analyzed the data on these workers. Among white men, nine myeloma-related deaths had occurred after 1965, whereas 6.3 would have been expected from the appropriately adjusted national rates. Gilbert and Marks also performed an internally standardized analysis by exposure category; in that analysis, three deaths from myeloma were recorded among white men who had been employed for at least two years and who had had an accumulated exposure level of at least 5 rem two years before they were at risk; 1.1 deaths would have been expected in this group. These values are used in Table 2, since they seem to reflect most accurately the outcome of the population at risk. The three men who died from

Table 2. Observed and Expected Cases of Myeloma in Atomic-Bomb Survivors and Cohorts Receiving Occupational Exposures to Radiation.

Cohort	Major Type of Radiation	No. of Cases Observed	No. of Cases Expected	P Value (Two-Sided)	90% Confidence Interval for Risk Ratio	Reference
Atomic-bomb survivors exposed to ≥100 rads	γ-rays, fast neutrons	5	1.59	0.03	1.3–14.0	Ichimaru et al.[13]
Hanford workers (≥5 rem)	γ-rays, α-panicles	3	1.10	0.19	0.74–7.0	Gilbert and Marks[16]
Windscale workers	γ-rays, α-panicles	4	1.00	0.038	1.4–9.2	Dolphin[17]
Radium-dial painters	α-panicles	6	0.86	0.0005	3.0–13.8	Stehney AF. Personal communication; Polednak et al.[18]
Uranium millers	α-particles, γ-rays	1	0.20	0.36	0.26–23.7	Archer et al.[21]
Uranium miners	α-particles, γ-rays	0	0.07	—	0–42.9	Wagoner et al.[22]
American radiologists	x-rays, γ-rays	11	7.91	0.28	0.8–3.0	Matanoski GM. Personal communication
British radiologists	x-rays, γ-rays	0	1.04	—	0–2.9	Smith and Doll"
All occupational exposures	—	25	12.18	0.002	1.4–2.9	—

myeloma actually had considerably higher total doses (34.9, 29.4, and 20.0 rem) that had been accumulated many years before myeloma was diagnosed (total duration of employment, 20, 19, and 17 years, respectively), so that a test for trend or a longer lag period between exposure and risk period would serve only to enhance the level of statistical significance.

An early report from Windscale[17] also suggested a link between radiation and myeloma. This study omitted retired workers and exworkers, and in view of the long latency period and late age distribution, some of the myelomas may well have been missed. However, four cases were diagnosed in workers while they were still employed. Only one myeloma would have been expected; the observed number is significant at the 5 per cent level (P = 0.038), although it was not reported as such. Furthermore, three of the four workers had had prolonged exposure to radiation (total service, 25, 11, and eight years) and appreciable cumulative doses (59, 3.3, and 4 rem, respectively).

Radium-Dial Painters

In a registry of 3600 radium-exposed persons that was compiled at the Argonne National Laboratory, eight deaths from myeloma were found (Stehney AF. Personal communication). These cases were identified only by examination of death certificates, and it is possible that osteoporosis and bone necrosis associated with the direct skeletal effects of radium influenced the diagnosis of myelomatosis; however, all deaths occurred after 1959, so that any diagnosis would probably have been confirmed by serum paraprotein identification or bone-marrow puncture or both. None of these deaths occurred among the subgroup of 634 women in a cohort of radium-dial painters, ascertained solely from employment lists, on which Polednak et al.[18] recently reported. However, six myeloma-related deaths occurred among dial painters who had worked in the industry before 1929, and five were among women, who constitute the vast majority of dial painters. The other two persons who died were a chemist and a woman who became a dial painter in 1944. Polednak et al.[18] stated that about 1400 female workers in radium-dial plants had been identified and that the United States Bureau of Labor Statistics had estimated that "not more than 2000 persons" had worked in radium-dial plants from their inception to 1929. If one assumes that all myeloma-related deaths among these workers have been recorded, that the age distribution in the cohort reported represented that in the entire work force, and that deaths from myeloma in the general population constituted 35 per cent of the deaths in the group with lymphomas and myelomas coded according to the International Classification of Diseases (ICD) as 200, 202, or 203, one would expect fewer than 0.86 deaths from myeloma among all workers in radium-dial plants. It may seem surprising that no deaths occurred in the cohort ascertained from employment records. However, if the total population of workers is assumed to be 2000, the probability that no deaths would occur in that cohort by chance alone is slightly greater than 10 per cent; thus, the finding is not highly exceptional.

Uranium Miners *and* Millers

The excess of lung cancer in uranium miners and millers has been studied in some detail.[19,20] However, little information is available about other cancers in this group. In a study of all deaths from cancer among uranium millers, Archer et al.[21] listed one death due to myelomatosis and 1.02 deaths expected among all the hematopoietic and lymphatic diseases coded as ICD 200 to 203 and 205 (sixth revision). In 1965, myeloma accounted for 20 per cent of these deaths in American

men, so that 0.20 expected deaths from myeloma is the estimated figure for this cohort. An earlier report from the same research group also considered uranium **miners.**[22] **No** deaths from myeloma were reported among white uranium miners with five **or** more years xperience, whereas an estimate of 0.07 expected deaths from this cause was obtained in the manner outlined above from the report of 0.6 expected deaths due to leukemia, lymphoma, and myeloma (ICD 200 to 205).

Radiologists

Lewis[5] first reported an excess of myelomatosis in American radiologists. His analysis showed five myeloma-related deaths as compared with 1.01 expected deaths. Matanoski et al.[23] reaffirmed this observation in a large study of radiologists and other physicians, including the radiologists studied by Lewis, and presented combined totals for myelomas and lymphomas. Dr. Matanoski has generously supplied further details about the myelomas (personal communication). In all cohorts studied from 1920 to 1969, 11 deaths from myelomatosis occurred among radiologists; this figure can be compared with that of 4.58 expected deaths when the standard taken is the group of American white men, **or** with 7.91 expected deaths if the comparison is standardized internally within the cohort of all 30,132 physicians, including 6518 radiologists. (This expected number also includes deaths **from** mycosis fungoides [ICD 205, seventh revision], and thus it is slightly too large. In fact, two such cases were observed in addition to the 11 myelomas.) Because myeloma is more likely to be ascertained in physicians that in nonphysicians, the larger value is presented in Table 2. (The difference between these two expected values is partly due to the fact that the latter value arises from an internal standardization. The expected number of myelomas in radiologists is 6.8 when all other physicians are taken as the reference population. This figure may still be high, as some of the other physicians may have had higher than average exposure to radiation.)

Court Brown and Doll[24] reported on cancer among 1381 British radiologists. In follow-up to 1977, Smith and Doll[25] found no myeloma-related deaths, compared with an expected figure **of** 1.04. This number was compiled with the correct national death rates from 1951 onward and the death rates from 1951 to 1955 for earlier periods; in view of the steady increase in reported deaths from myeloma, the figure of 1.04 is likely to be slightly too high. However, one radiologist is known to have died of myeloma less than a year after the close of the study, and another had myeloma in 1972 when he committed suicide. Both these members entered the study before 1921, when exposure to radiation was probably much higher.

Diagnostic and Therapeutic irradiation

The data accruing from diagnostic and therapeutic exposures are summarized in Table 3.

Patients Receiving Thorotrast

Over 4000 patients given thorium oxide (Thorotrast) as a contrast medium for angiography have been followed up in Danish, German, and Portuguese cohorts. According to Kaul and Noffz,[26] a 25-ml injection of thorium oxide produces a continuous dose of 9 rads per year in the form of a-rays to the bone marrow. The main concern of these studies was the large excess of liver cancers. However, seven myelomas were reported in the three cohorts[27-29] (Table 4). Faber[27] reported four of these tumors in the Danish group, as compared with 0.77 expected cases. Expected numbers were not given in the other cohorts. However, since the age distribution and follow-up time in the cohorts were similar, expected numbers can be estimated (Table 4) from the cohort sizes and from differences in national death rates. Data from Spain

Table 3. Observed and Expected Myelomas in Cohorts Receiving Diagnostic and Therapeutic Radiation.

COHORT	MAJOR TYPE OF RADIATION	NO OF CASES OBSERVED	NO OF CASES EXPECTED	P VALUE (Two-Slotd)	90% CONFIDENCE INTERVAL FOR RISK RATIO	REFERENCE
Thorotrast angiography						
Denmark	a-particles	4	0.77	0.015	1.8–11.9	Faber[27]
Germany	a-particles	2	0.93	0.48	0.4–6.8	van Kaick et al.[28]
Portugal	a-particles	1	0.16	0.30	0.3–30.0	da Motta et al.[29]
Spondylitis						
Britain	x-rays	3	1.87	—	0.4–4.2	Smith and Doll (ref. 31 and personal comunication)
Germany	α-particles	0	0.25	—	0–12.0	Spiess et al.[32]
Fluoroscopy	x-rays	0	0.39	—	0–7.7	Boice[33]
Benign gynecologic disorders. Connecticut						
No radium	x-rays	3	1.10	0.19	0.74–7.0	Wagoner[34]
Radium	γ-rays	7	0.88	0.44	0.4–7.2	Wagoner[38]
Metropathia hemorrhagica	x-rays	5	2.09	0.12	0.94–5.0	Smith and Doll (ref. 39 and personal communication)
Uterine cancer, Connecticut	γ-rays, x-rays	1	2.92	0.42	0.02–1.62	Wagoner[35]
Cervical cancer	γ-rays. x-rays	2	7.19	0.03	0.05–0.81	Boice and Hutchison[40]

Table 4. Deaths from Myeloma in Patients Given Thorotrast (Thorium Oxide).

Cohort	No. of Patients	National Myeloma Death Rates*	No. of Expected Deaths	No. of Observed Deaths	Follow-up Date	Reference
		×10⁻⁵/yr				
Danish	1026	2.95	0.77	4	~3/76	Faber[27]
German	1964	1.86	0.93	2	9/75	van Kaick et al.[28]
Portuguese	1052	*0.59* †	0.16	1	12/76	da Motta et al.[29]

*Average of rates from 1968 to 1974.

†Since data from Portugal were not available, comparable data from Zaragoza, Spain. were used.

were used for Portugal, since detailed Portuguese mortality data were not available. Rates represent an average of the rates from 1968 to 1974, standardized to the European population. Data were obtained from World Health Organization magnetic tapes.

Similar estimates were obtained when adjustments were based on incidence data from the Danish cancer registry, from Hamburg and Saarland combined for Germany, and from Zaragoza, Spain, for the Portuguese series.[30] The low death rate used for the Portuguese series suggests underascertainment of myeloma in the general population of this country, and the expected numbers estimated in Tables 3 and 4 might prove to be too low in this series if the recorded causes of death in members of this cohort were determined by a more thorough investigation than is normally conducted.

Irradiation for Spondylitis

Court Brown and Doll[2] studied a British cohort of 14,111 men and women given x-ray therapy for ankylosing spondylitis. Two cases of myelomatosis were found when the group was followed up to 1963. Further follow-up to January 1, 1970, after a single course of radiation[31] uncovered a total of three cases of myeloma, whereas 1.87 would have been expected from the rates in England and Wales (Smith PG, Doll R. Personal communication). These cases occurred eight, 16, and 17 years after treatment.

A smaller cohort of 612 adults treated with radium 224 for tuberculosis, ankylosing spondylitis, and a few other diseases was investigated by Spiess et al.[32] No cases of myeloma were manifest, and expected numbers were not given for myeloma, but data on expected cases are available for other sites. With the expected number of intestinal and rectal cancers and the age-adjusted rates from the Hamburg cancer registry used for standardization,[30] an estimate of 0.25 expected myelomas was obtained. Similar results are obtained if the estimate is derived from the expected number of cases of cancer at another common site, such as the stomach or lung.

Fluoroscopy

Boice[33] reported on a cohort of 1047 women with tuberculosis who had been monitored weekly by fluoroscopy after treatment with pneumothorax. Individual exposures averaged 1.5 rads, and the mean cumulative dose was about 150 rads to the breast tissue. No myelomas were seen, whereas 0.39 would have been expected if myeloma had accounted for 24 per cent of the expected 1.6 myelomas and lymphomas that are coded as ICD 200 to 203, as it did in the Connecticut cancer registry.[30]

Irradiation for Gynecologic Disorders

Several cohorts of women irradiated for gynecologic disorders have been described. An excess of myeloid leukemia has been found in most large cohorts given uterine irradiation for benign conditions, but no surplus has been found among women given a higher dose of intense radiation for uterine cancers. Smith[34] has reviewed these data and discussed the explanation for this phenomenon, proposed earlier by Hutchison, that potentially leukemogenic cells are killed by intense radiation. Further support for this theory, which implies that a reduction in dose from high to intermediate levels will not produce a proportional reduction in incidence, was provided by Mole's analysis of other cancer sites[35,36] and by the experiments of Major and Mole[37] on myeloid leukemia in x-irradiated mice.

The available evidence on the incidence of myelomatosis is consistent with this hypothesis of nonlinearity. Excess cases were found among patients given moderate levels of radiation for benign conditions, but not in patients irradiated for uterine neoplasms. In a study of 1893 women in Connecticut who were irradiated for benign gynecologic disorders from 1935 to 1964 and followed until 1967, Wagoner[38] reported 2 myelomas (as compared with 0.88 expected cases) in patients treated with radium (mean marrow dose, 40 to 126 rads of γ-rays) and three observed cases (compared with 1.10 expected) in patients given x-ray therapy (mean marrow dose, 100 to 300 rads). Smith and Doll[39] reported three cases of myeloma among 2068 women given x-irradiation (mean marrow dose, 70 to 190 rads) for metropathia hemorrhagica. Further follow-up to November 1, 1979, (Smith PG. Personal communication) yielded a total of 5 myelomas, whereas 2.09 such tumors would have been expected. These cases occurred 19, 22, 22, 23, and 27 years after radiotherapy. Thus, moderate levels of radiation produced 10 cases of myeloma in these cohorts, although 4.07 would have been expected ($P = 0.018$).

However, women given higher levels of radiation for uterine cancer had a deficit of myelomas. Wagoner" found one myeloma (as compared with 2.92 expected cases) in an irradiated cohort of 7835 women with uterine neoplasias in Connecticut (mean marrow dose, 300 to 1500 rads). In a large international survey of almost 30,000 women irradiated for cervical cancer, Boice and Hutchison[40] reported two cases of myeloma, whereas 7.79 would have been expected. Follow-up continued for only 10 years, so that the lack of an excess is not unexpected. However, the deficiency of cases is of interest, since there were three cases

observed and **10.71** expected (P = **0.012)** in cohorts of women intensely irradiated for uterine cancers.

DISCUSSION

aution is needed in interpreting this analysis, since there are many possible sources of error. Numbers of expected cases were estimated indirectly, although when alternative methods were available I tended to act conservatively and choose the larger values. Any resulting inaccuracy in the expected numbers will be small and will not materially affect the overall conclusions.

4 more serious concern involves possible biases introduced by a more complete ascertainment of deaths due to myelomatosis in the exposed cohorts than would be found in the general population. The possibility that ascertainment of deaths from myeloma has been incomplete in the general population is suggested by improvements in diagnostic procedures over the past **40** years owing to bone-marrow puncture and electrophoresis, and that possibility is reinforced by the social-class gradient" (standardized mortality ratio for Social Class I (professional] men aged 15 to **64** years, **143)** and by the sharp secular trends of the past 30 years. Thus, populations under greater surveillance for cancer may have misleadingly higher rates. This bias may be an important factor in radiation .workers, dial painters, British radiologists, and possibly Portuguese patients given Thorotrast for whom the low national death rates also suggest underascertainment in the general population. However, r ٦ within the cohort of radiation workers at Han- and Windscale, persons with myeloma had higher cumulative exposures, and it seems unlikely that they would have received more thorough diagnoses than did their fellow workers. I compared American radiologists with other physicians, *so* that ascertainment would be similar in both groups, though possibly more complete among physicians than in the general population. Expected numbers of cases were determined internally within the cohort of atomic-bomb survivors; thus, ascertainment bias should not have occurred in that group. It is difficult to assess the degrees of bias in the other groups, although they are likely to be minimal, since the cases were not in general followed particularly intensively, and since myeloma was not an expected consequence of the exposure to radiation. Furthermore, myeloma-related deaths in these cohorts were published incidentally with minimal further comments.

Bias associated with the selection of favorable cohorts was minimized through attempts to include every cohort of radiation-exposed persons for which a list of observed cancers has been published.

The data are summarized in Table 3. There is a clear excess of myeloma among persons exposed to radiation **(53** cases observed, **32.92** expected; **P = 0.0016).** This conclusion is not dependent on the results from any one cohort, and it will withstand the r tion of any single set of data. The most striking naly is the deficit of myeloma observed in two large cohorts of women who received intense irradiation for uterine carcinomas (three cases observed, **10.17** expected; P = **0.012).** In view of the highly significant increase in myeloma in all other cohorts combined (50 cases observed, **22.21** expected; $P = 2\times10^{-7}$), the decrease in this group cannot be ignored. It remains uncertain whether the decrease is attributable to a protective effect of intense cytotoxic irradiation or to other factors, such as exclusion of patients with myeloma from the cohort, incomplete ascertainment of myeloma, or a lowered susceptibility to this disease. Nevertheless, this deficit of myeloma, the absence of an excess of leukemia in these cohorts, and the decreased leukemogenicity of radiation at high doses in animals all suggest that the carcinogenic potential of intense radiation is different from that of less concentrated exposure, and these factors provide a justification for treating these cohorts separately. The data from all other cohorts provide strong and internally consistent evidence for the thesis that radiation can cause myelomatosis.

Table 5. Summary of Data on Observed and Expected Myelomas According to Type of Radiation.

GROUP	NO. OF CASES OBSERVED	NO. OF CASES EXPECTED	P VALUE (TWO-SIDED)	90% CONFIDENCE INTERVAL FOR RISK RATIO
All uterine cancers	**3**	**10.71**	**0.012**	**0.08–0.72**
All cohorts receiving appreciable α-irradiation	**14**	**3.24**	2×10^{-5}	**2.6–6.8**
All cohorts receiving diagnostic or therapeutic γ-rays or x-rays. except uterine cancers	**13**	**6.33**	**0.026**	**1.2–3.3**
All cohorts receiving only x-rays	**11**	**5.45**	**0.017**	**1.1–3.3**
All cohorts except uterine cancers	**50**	**22.21**	2×10^{-7}	**1.7–2.8**
All cohorts	**53**	**32.92**	**0.0016**	**1.3–2.0**

Although accurate estimates of the degree of marrow exposure are unavailable for many cohorts, the variations in the 90 per cent confidence intervals for the risk ratios are, for the most part, .in qualitative agreement with the likely differences in exposure. The highest risk ratios were found among persons receiving internal doses of a-emitters **(14** cases observed, **3.24** expected; risk ratio, **2.6** to **6.8).** In this group, which consists primarily of dial painters and patients who received Thorotrast, the effect of a small total dose of radiation may be magnified considerably, since the radionuclides involved are in fact deposited in bone tissue, so that high-linear-energy-transfer a-emission effectively irradiates the marrow. This means of exposure may also be an important factor among workers in the nuclear industry, especially in plutonium-reprocessing plants, for whom the risk ratio (seven cases observed, **2.10** expected; risk ratio, 1.6 to **6.3)** was higher than one might predict from the recorded exposures to external y-rays. Some evidence **(13** cases observed, **6.3** expected; P = **0.026)** was also found of induction of myeloma by moderate thera-

peutic and diagnostic levels (70 to 300 rads to the marrow) of y-rays and x-rays, whereas the lesser average exposure likely among radiologists accords with a minimal excess risk that is not statistically significant and could well be negligible.

Although these data do not permit an accurate computation of excess risk as a function of time from exposure, a review of the cases for which the time from exposure is available suggests that radiogenic myelomatosis usually does not appear until at least 10 years after exposure. It will be interesting to see whether the deficit of myeloma in patients with uterine cancer persists with longer follow-up.

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