Conf-830101--6

82-11 Health Phys. Conference

CONF-830101--6

DE83 009523

MULTIPLE MYELOMA, LEUKEMIA, AND BREAST CANCER AMONG THE U.S. RADIUM DIAL WORKERS

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ABSTRACT

The relationships of radium exposure to mortality from multiple myeloma, leukemia, and breast cancer were studied in three cohorts of female dial workers defined by year of first employment. Mortality was compared with that expected from U.S. white female rates, with and without adjustment for local mortality rates. Dose-response relationships of these cancers to systemic intake of radium were determined in workers whose body burdens had been measured in vivo since 1955. Incident cases of multiple myeloma and leukemia were also studied. A three-fold excess risk of multiple myeloma occurred in the pre-1930 cohort; however, analyses of body burdens and durations of employment suggest that external radiation was more likely to have been responsible than was internal radium. Leukemia incidence and mortality have not been elevated overall among the female dial workers, either in the pre-1930 or the post-1930 cohorts, but cases have tended to occur early and in subjects with higher body burdens. Extensive analyses of breast cancer data have uncovered several observations weighing against a causal interpretation of the association between radium and breast cancer.

Introduction

The radium dial painters have now experienced significant mortality from cancers other than the bone sarcomas and the carcinomas of paranasal sinuses and mastoid air cells long known to be radium induced. Among these other cancers, the most strongly suspected of being radium induced are multiple myeloma (1), leukemia (2), and breast cancer (3).

In this paper we reevaluate the evidence concerning the role of radium in the etiology of these neoplasms. Some results concerning these tumors are being published in extended form along with a more detailed description of methods (4,5).

Methods

Study cohorts. The study population consisted of located women employed in the U.S. radium dial painting industry prior to 1970. Subcohorts have been defined on year of first employment (pre-1930, 1930-1949, 1950-1969), and on radium measurement status (measured living 1955+, or not). The pre-1930 cohort worked primarily in Connecticut, Illinois, and New Jersey. Illinois, Massachusetts, New York, and Pennsylvania contributed the great majority of workers to the 1930-1949 cohort. The radium body burdens of approximately half the members of each cohort have been measured in vivo since 1954. We report the mortality experience of measured cohorts beginning two years after measurement. Otherwise mortality or incidence from beginning of employment through 1979 are reported. Table 1 describes the relevant characteristics of these cohorts.

Expected mortality and incidence. Mortality analyses were carried out using an 8th ICD version of the Monson program (6), modified to permit entry in 1915. Expected myeloma mortality was manually generated from published U.S. vital statistics, using rates and person-year tables directly for the 1970's, and proportional mortality within the broader Monson ICD categories (202, 203, 208 in the 8th ICD; 202, 203, and 205 in the 7th ICD) back to 1950, prior to which expectations are not available. Expected leukemia incidence was derived from Connecticut Cancer Registry data incorporated in the Monson program. Myeloma incidence expectations were derived by multiplying expected mortality by the ratio (1.4058) of incidence to mortality in U.S. white females covered by U.S. tumor registries between 1973 and 1977 (7). Calculation of expected multiple myeloma is complex and is described in detail elsewhere (5); expected values published for this cohort (1) on the basis of an earlier report (2) are incorrect.

Radium intake estimates. "Initial systemic intakes" were calculated by extrapolating ^{226}Ra body contents at measurement back to time of exposure using the radium retention function of Norris et al. (8). ^{228}Ra exposure was estimated from ^{226}Ra exposure and knowledge of the proportions of ^{226}Ra and ^{228}Ra over time and among companies. Initial intake estimates used here weight ^{226}Ra and ^{228}Ra equally. Analyses are restricted to subjects measured living in 1955 or later, unless stated otherwise.

Statistical methods. Tests of significance are based on the Poisson distribution; exact tests of the deviation of an observed value from expected, and of the homogeneity of two Poisson processes (given the total observed and the two calculated expected values) are both used (9). Confidence limits are based on tabulated (10) limit multipliers. A large sample approximation for the rank sum test has been used to generate normal z scores.

The effect on overall expected mortality of regional mortality rates was determined by adjusting expected mortality to the weighted average of total age-adjusted county rates for 1950-1969 (11), for counties in which major work places were located (>80% of the population). Other workers were assumed to have the same relative risks as the workers at the major sites. We also calculated a maximum dilutive effect of migration using data from Polissar (12) based on national average migration rates and a 30-year latent period for county areas.

Results

Multiple myeloma. Table 2 shows that multiple myeloma mortality in the pre-1930 cohort is significantly elevated. This three-fold excess is slightly reduced by adjustments for regional mortality (Table 3), but remains statistically significant. Table 4 shows incidence data for all dial workers and for those measured living. A significant, approximately three-fold, relative risk remains in the pre-1930 cohort. The elevation in mortality would not be statistically significant were not one case improperly certified to multiple myeloma. However, this case was properly an incident case, so the overall findings are not significantly affected.

Four of the incident cases, all pre-1930, had been measured living. Their radium body burdens were variable, but all four had worked at least a year. The probability of this occurring by chance is .075, when the expected employment durations below and above 50 weeks were in the ratio 0.35:0.38. On the other hand the distribution of expected systemic radium intakes below and above 5 µCi was in the ratio 0.47:0.25, while the observed ratio was 2:2 (p = .43). Employment durations of the other two pre-1930 cases were two weeks and "unknown." Duration of employment, a surrogate for external gamma radiation exposure, rather than internal radium burdens, would appear to be the more likely explanation for the association between dial work and multiple myeloma.

Leukemia. Deaths due to leukemias in the pre-1930 cohort (Table 2) are slightly fewer than expected. A modest but non-significant excess appears in the 1930-1949 cohort. Adjustment of expected values for regional mortality rates and migration effects further reduces the observed/expected ratio for leukemia. Leukemia incidence is shown in Table 4; the results described for mortality continue to hold.

Table 5 describes leukemia incidence by decade of onset and by type of leukemia. Two cases occur in the 1930's, a statistically significant excess through 1939. In addition, the 3 of the 4 cases measured (not necessarily while living) in the pre-1930 cohort had relatively high radium intakes (z = +2.244, by rank sum test). However, the high radium burdens were almost perfectly correlated with extended periods of employment (676, 676, and 78 weeks; z = +1.980). Further, one of these high burden cases was a chronic lymphocytic leukemia, a type not considered to be radiation-induced.

In general, the distribution of types of leukemia across all cohorts was as expected from proportional incidence: chronic lymphocytic, observed 4, expected 2.3; acute myeloid, observed 3, expected 3.1; chronic myeloid, observed 1, expected 1.5; other and unspecified, observed 1, expected 0.5. No clear excess of myeloid leukemia appears overall or in the pre-1930 cohort.

An excess of leukemia is predicted by the ICRP risk model (13). Table 6 shows observed and predicted leukemias after body burden measurement for the subjects measured living. The table is based on estimates of bone marrow dose from alpha radiation (4) and a quality factor of 20. Numbers are small, but only 2 leukemias have been seen where 4.7 are predicted (p = .154).

Breast cancer. The published finding that breast cancer appeared to be induced by radium, rather than concurrent gamma exposure, was based upon the dose-response relationship with radium intake but not with duration of employment, in the presence of elevated rates overall in the pre-1930 cohort (3). Several arguments against the reality of the overall excess and against a causal nature for the observed association follow.

Breast cancer mortality was significantly elevated in the pre-1930 cohort (Table 2). When expected values are adjusted for regional mortality and migration (Table 3), the risk ratios are considerably reduced, and the excess is no longer statistically significant. The excess is 20% or less, for a comparison of employed women with all white females. Further, we observe (Table 3) that the excess holds before adjustment for county mortality in the 1930-1949 and 1950-1969 cohorts, cohorts in which radium exposures were a hundred-fold lower than in the pre-1930 cohort. In Table 7, Ottawa, Illinois, the one work place with substantial expectations both pre- and post-1930, shows a clearly constant or increased risk in the 1930-1949 cohort relative to the pre-1930 cohort.

Table 7 also shows a major inconsistency in findings among the work places. The Waterbury, Connecticut, pre-1930 work force (the post-1930 workforce was very small) had extremely low breast cancer rates, approximately 15% of expected. This is only 5-10% of the rates observed in the New Jersey and Illinois populations. This heterogeneity is very highly statistically significant.

Table 8 describes breast cancer risk ratios by age at first exposure. Women under 20 have been described as being at excess risk of breast cancer following exposure to external ionizing radiation (14). No suggestion of any effect occurs, except among the 1930-49 cohort in which radium exposure was minimal; that excess did not persist in the measured cases.

Table 9 summarizes the dose-response data: a clear and highly significant dose-response relationship of breast cancer with systemic radium intake, but not with duration of employment, appears. An apparent and marginally significant dose-response relationship also occurs in the 1930-1949 cohort, but at absolute dose levels a hundred-fold lower than in the pre-1930 cohort. Table 10 further demonstrates that mortality outcomes not currently under suspicion of being induced by radium, heart disease and stroke, also show dose-response relationships to radium.

Discussion

Multiple myeloma. The conclusion (1) that persons receiving internal doses of alpha emitters have a higher risk of multiple myeloma than persons exposed to external ionizing radiation rests in large part on these cases among the radium dial workers. Appropriate calculation of expected values, however, reduces the risk ratio to 2.84 in the dial workers, a risk close to that observed among individuals exposed only to gamma or x rays, and about one-half of that previously reported for the radium dial workers (1).

Further, review of employment durations and systemic radium intakes among the pre-1930 female radium dial workers suggests that duration of employment rather than radium intake is closely correlated with multiple myeloma. Duration of employment for the dial workers is a surrogate for external gamma irradiation.

More complete ascertainment of multiple myeloma cases in the early years among populations exposed to internal emitters is possible. Such an effect was recently described in one county with excellent diagnostic facilities (15). In our experience, radium-induced changes in the appearance of bone observed on x-ray examination frequently lead to mention of possible myeloma in the medical records.

In summary, there appears to be no reason to ascribe the excess multiple myeloma in the dial workers to internal alpha emitters rather than to external gamma irradiation, and possibly to a higher index of clinical suspicion resulting from radium-induced bone changes.

Leukemia. Leukemia mortality and incidence from exposure in the 1920's through 1979 has been lower than expected in the pre-1930 dial workers with calculated risk ratios in the range 0.61 to 0.74. Incident leukemia cases occurred less frequently than expected based on ICRP risk factors in the cases measured since 1954. However, two cases occurred significantly early, and there is an appearance of a dose-response relationship with both employment duration and radium intake. Blood dyscrasias were a prominent finding in early radium studies. Loutit (16) reviewed early case descriptions and suggested that they supported diagnoses of malignant myelosclerosis, even possibly erythremic myelosis. Loutit also reviewed three more recent radium cases, all males, and suggested that they all could be classed as aleukemic leukemia. Polednak also suggested that some fatal aplastic anemias may have been aleukemic leukemia (2).

We regard the question of a leukemogenic effect of internal body burdens of radium in the first 20 years after exposure as still open. It is clear, however, that there has been no overall excess leukemia, and especially no excess in the period 20 to 55 years after exposure. If the early and/or high dose cases are assumed to be radium induced, then there is a clear shortfall in the number of leukemia cases in the remainder of the pre-1930 cohort.

We have underway further investigations of leukemia, especially erythrocytic leukemia, in male radium subjects. Males and females may not respond similarly.

Breast cancer. The evidence presented above weighs strongly against an etiologic role of radium for breast cancer. That some breast cancer may have occurred due to external radiation exposures is not at issue. The arguments against an etiologic role for radium can be summarized as follows: (a) the overall excess of breast cancer in the pre-1930 cohort is reduced to statistical insignificance when adjustments for county mortality are carried out; (b) the post-1930 cohorts, and especially the directly comparable Ottawa, Illinois, cohort, show high breast cancer risks despite radium exposures a hundred-fold lower; (c) one of the three major work forces had extremely low breast cancer rates, very statistically significantly different from the other two work places; (d) there is no suggestion of excess risk in women exposed under age 20, as expected from external radiation studies; (e) although a significant dose-response relationship occurs in the pre-1930 cohort, it also appears in the 1930-1949 cohort at absolute radium intake levels a hundred-fold lower, and (f) crude dose-response relationships of radium intake to arteriosclerotic heart disease and cerebrovascular disease exist, relationships which would not be immediately taken as suggesting an etiologic relationship.

Further analyses of incident breast cancer, and of pre- and postmenopausal breast cancer separately, are planned. Of more interest, and a priority item for future research, are the correlations of risk factors for heart disease, stroke, and breast cancer with intake of radium and its retention over the adult lifespan.

Acknowledgments

This research was performed under U.S. Department of Energy contract No. W-31-109-ENG-38. The technical assistance of Georgia A. Anast, and the secretarial assistance of Marie C. D'Arpa are gratefully acknowledged.

References

(1) J. Cuzick, "Radiation-induced Myelomatosis," New England Journal of Medicine, 304, pp. 204-210 (1981).

(2) A. P. Polednak, A. F. Stehney and R. E. Rowland, "Mortality Among Women First Employed Before 1930 in the U.S. Radium Dial Painting Industry," American Journal of Epidemiology, 107, pp. 179-195 (1978).

(3) E. E. Adams and A. M. Brues, "Breast Cancer in Female Radium Dial Workers First Employed Before 1930," Journal of Occupational Medicine, 22, pp. 583-587 (1980).

(4) F. W. Spiers, H. F. Lucas, J. Rundo and G. A. Anast, "Leukaemia Incidence in the U. S. Dial Workers," Health Physics, in press.

(5) J. H. Stebbings, H. F. Lucas and A. F. Stehney, "Mortality from Cancers of Major Sites Among Female Radium Dial Workers," submitted for publication.

(6) R. R. Monson, "Analysis of Relative Survival and Proportional Mortality," Computers and Biomedical Research, 7, pp. 325-332 (1974).

(7) "Surveillance, Epidemiology, and End Results: Incidence and Mortality Data, 1973-1977," National Cancer Institute Monograph 57. NIH Publication No. 81-2330, U.S. Government Printing Office, Washington, 1981.

(8) W. P. Norris, T. W. Speckman and P. F. Gustafson, "Studies of the Metabolism of Radium in Men," American Journal of Roentgenology, 73, pp. 785-802 (1955).

(9) M. E. Ginevan, "A Poisson Trials Approach to Interpopulation Comparisons of Cause of Death Data," Environmental Research, 25, pp. 147-159 (1981).

(10) A. M. Lilienfeld, E. Pedersen and J. E. Dowd, "Cancer Epidemiology: Methods of Study," Baltimore: The Johns Hopkins Press, 1967.

(11) T. J. Mason and F. W. McKay, "U. S. Cancer Mortality by County: 1950-1969," U.S. Government Printing Office, Washington, 1974.

(12) J. Polissar, "The Effect of Migration on Comparison of Disease Rates in Geographic Studies in the United States," American Journal of Epidemiology, 111, pp. 175-182 (1980).

(13) "Recommendations of The International Commission on Radiological Protection," ICRP Publication 26, Annals of the ICRP, 1, 3 (1977).

(14) "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation," (BEIR III). National Academy of Sciences, Washington, 1980.

(15) A. Linos, R. A. Kyle, W. M. O'Fallon and L. T. Kurland, "Incidence and Secular Trend of Multiple Myeloma in Olmstead County, Minnesota: 1965-77," Journal of the National Cancer Institute, 66, 17-20 (1981).

(16) J. F. Loutit, "Malignancy from Radium," The British Journal of Cancer, 24, pp. 195-207 (1970).

Table 1. Female dial worker follow-up statistics.

	All dial workers			Measured dial workers	
	<1930	1930-1949	1950-1969	<1930	1930-1949
Person-years of survival	60708	41710	5108	8756	2952
Number of persons	1285	1185	226	693	561
Average age at entry	19.9	24.3	30.7	60.9	53.5
Average year of entry	1923	1943	1956	1965	1974
Average age at death	59.1	56.6	52.7	70.4	59.6
Average year of death	1959	1968	1970	1972	1975
Deaths	626	210	21	197	28

Table 2. Observed and expected deaths from multiple myeloma, leukemia, and breast cancer in female dial workers.

Cause of death (8th ICD No.)	Observed	Expected[a]	O/E[b]	p (≥ obs.)[c]	95% CI[d]
Multiple myeloma (203)[e]					
< 1930	5	1.50	3.33	.019	1.08- 7.76
1930-1949	1	0.58	1.73	.44	0.04- 9.64
1950-1969	0	0.07	0.00	1.0	0.00-42.86
All years	6	2.15	2.79	.023	1.02- 6.08
Leukemia (204-207)					
<1930	3	4.10	0.73	.78	0.15- 2.13
1930-1949	4	1.81	2.21	.11	0.60- 5.66
1950-1969	0	0.22	0.00	1.0	0.00-13.64
All years	7	6.13	1.14	.42	0.46- 2.35
Breast cancer (174)					
<1930	36	25.09	1.44	.024	1.01- 2.00
1930-1949	15	13.51	1.11	.38	0.62- 1.83
1950-1969	3	1.64	1.83	.23	0.38- 5.34
All years	54	40.24	1.34	.022	1.01- 1.76

[a]Based on cause-, age- and calendar-time-specific death rates for U.S. white females, except for multiple myeloma before 1970 (see text).
[b]Observed/expected.
[c]By exact Poisson test.
[d]CI refers to confidence interval.
[e]Expectations are 1950+ only.

Table 3. Risk ratios for female dial workers adjusted for mortality rates (1950-1969) in county of exposure and for migration.[a]

			Adjusted for			
			County rates		County rates and migration	
Cause of death	Observed	O/E	O/E	95% CI	O/E	95% CI
Multiple myeloma						
<1930	5	3.33	3.19	1.03-7.43	3.09	1.00-7.20
1930-1949	1	1.73	1.56	0.04-8.67	1.45	0.04-8.05
All years	6	2.79	2.63	0.97-5.73	2.52	0.93-5.50
Leukemia						
<1930	3	0.73	0.66	0.14-1.91	0.61	0.13-1.78
1930-1949	4	2.21	1.93	0.52-4.93	1.76	0.48-4.51
All years	7	1.14	1.02	0.41-2.10	0.95	0.38-1.95
Breast cancer						
<1930	36	1.44	1.20	0.84-1.66	1.05	0.74-1.46
1930-1949	15	1.11	0.92	0.51-1.51	0.80	0.45-1.32
All years	54	1.34	1.12	0.85-1.47	0.99	0.74-1.30

[a] O/E and CI defined in footnotes, Table 2. Migration adjustments from Polissar (12) Table 2, for 30-year latency, county scale. "All sites" factor used for multiple myeloma. The small expectations in 1950-1969 cohort in the "all years" total have not been adjusted.

Table 4. Observed and expected incident cases of multiple myeloma and leukemia in female dial workers.[a]

	All dial workers				Measured dial workers			
	Obs.	Exp.	O/E	95% CI	Obs.	Exp.	O/E	95% CI
Multiple myeloma								
<1930	6	2.11	2.84	1.04-6.19	4	1.02	3.90	1.06-10.0
1930-1949	1	0.81	1.23	0.03-6.85	0	0.14	0.00	0.00-21.2
1950-1969	0	0.10	0.00	0.00-30.6	0	0.01	0.00	0.00-279.
All years	7	3.02	2.31	0.93-4.76	4	1.18	3.40	0.92-8.70
Leukemia								
<1930	4	5.44	0.74	0.20-1.88	2	2.04	0.98	0.12-3.54
1930-1949	4	2.27	1.76	0.48-4.51	0	0.27	0.00	0.00-11.2
1950-1969	1	0.26	3.79	0.10-21.1	0	0.02	0.00	0.00-120.
All years	9	7.97	1.13	0.52-2.14	2	2.33	0.86	0.10-3.10

[a] O/E and CI defined in footnotes, Table 2. Myeloma expected values in dial workers measured living since 1955 based on proportional mortality only.

Table 5. Fatal and incident leukemia cases by year of death or diagnosis.[a]

		Quinquennium of death									
Cohort		<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
<1930	Obs.		UN-2836 CM					CL-90			(AM-20)
	Exp.	.18	.11[b]	.16[b]	.21	.32	.41	.50	.63	.73	.86
1930-1949	Obs.						AM			AM-2	CL CL
	Exp.	.00	.01	.04	.11	.16	.20	.23	.29	.35	.43
1950-1969	Obs.									(CL)	
	Exp.					.01	.02	.03	.04	.05	.07

[a]Incident cases in parentheses. AM, acute myeloid; CM, chronic myeloid; CL, chronic lymphocytic; UN, unspecified. Best diagnosis is used. Systemic intake of radium in microcuries follows abbreviation if available.

[b]Probability of observing 2 or more cases, given 4, through 1939 is .0269, through 1944 .0606.

Table 6. Leukemias observed, and predicted using ICRP risk factors, in subjects measured living in 1955 or later.

Skeletal dose (rad)		Marrow		Predicted cases		
Range	Mean	dose (rad)	N	Radiation	Background	Observed
<100	20.4	1.054	489	.076	1.42	0
100- 499	235.3	12.18	114	.205	.38	1
500-2499	1194.4	61.83	46	.421	.12	1
2500-4999	3589	185.8	25	.688	.07	0
5000+	8512	440.7	19	1.239	.06	0
Total			693	2.63	2.05	2[a]

[a]Probability of observing 2 or less, given 4.68 expected, is .1543.

Table 7. Breast cancer risk ratios for radium dial workers by factory.

	All cases: deaths 1915+				Measured cases:deaths 1957+			
	Before 1930		1930 - 1949		Before 1930		1930 - 1949	
Factory of work	Cases	O/E	Cases	O/E	Cases	O/E	Cases	O/E
All work places	36	1.44	15	1.11	11	1.36	6	3.15
Orange, New Jersey	13	1.74	-	-	1	0.58	-	-
Ottawa, Illinois	15	2.29	9	2.01	8	2.77	5	4.24
Waterbury, Connecticut	1	0.15	1	1.95	0	0.00	1	13.5
Probability[a]	.0002		.73		.0249		.96	

[a]Exact probability of occurrence of fewer or equal observed in Waterbury, given expected numbers and total of cases occurring. Probabilities for temporal cohorts combined: all cases, .0004; measured cases, .0392.

Table 8. Breast cancer risk ratios in female dial workers by age first employed.

	All cases: deaths 1915+				Measured cases:deaths 1957+			
	Before 1930		1930 - 1949		Before 1930		1930 - 1949	
Age first employed	Cases	O/E	Cases	O/E	Cases	O/E	Cases	O/E
<20	22	1.43	7	2.13	8	1.41	2	2.29
20-29	11	1.43	6	0.93	3	1.39	4	4.62
30	3	1.48	2	0.53	0	0.00	0	0.00
Probability[a]	.58		.049		.58		.85	

[a]Exact probability of occurrence of greater than or equal to observed in <20 years category, given expected numbers and total of cases occurring.

Table 9. Breast cancer risk ratios in measured cases by radium intake and duration of employment.

	Before 1930		1930 - 1949	
	Cases	O/E	Cases	O/E
Initial systemic radium intake (μCi)				
<0.5	0	0.00	1	0.90
0.5-4.9	2	0.63	5	6.50
5.0-49	3	1.52	-[b]	-
>50	6	6.59	-[b]	-
Prob. (>Obs.)[a]	.001		.046	
Weeks of employment				
<0-4	0	0.00	0	0.00
5-49	5	1.73	1	2.69
>50	6	1.43	5	3.57
Prob. (>Obs.)[a]	.54		.50	

[a]Probability of > observed in >50 categories, given total observed and the expected values in each category.
[b]Only 4 subjects at risk over 5 μCi.

Table 10. Cardiovascular and cerebrovascular mortality in pre-1930 measured female radium dial workers.

	Radium intake (μCi)			
	<50		50+	
	Cases	O/E	Cases	O/E
Arteriosclerotic heart disease	53	0.79	11	1.54
Cerebrovascular disease	12	0.50	4	1.60