An Epidemiologic Approach to Low-Level Radium 226 Exposure

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DEVELOPMENT of radiation protection standards for the general population has been difficult, primarily because of the lack of definitive information concerning dose-effect relationships at low levels of exposure. To clarify this problem, the Federal Radiation Council (*1*) has recommended that special attention be given to "epidemiological studies on humans exposed to doses sufficient to offer some probability that deleterious effects can be found." Martland (*2*) and others (*3, 4*) have documented numerous cases in which relatively high levels of radium 226 deposited in the human skeleton have produced malignant neoplasms. In 1958 Lucas and Ilcewicz (*5*) reported elevated radium 226 concentrations in a sizable number of public ground water supplies in Illinois. Subsequent investigations revealed the extensive occurrence of elevated radium 226 levels in Iowa ground water supplies as well. Marinelli (*6*) called attention to the human populations using these water supplies and pointed out the epidemiologic potential of such a group for low-level, dose-effect studies.

In 1962 the Division of Radiological Health of the Public Health Service, in cooperation with Argonne National Laboratory's Division of Radiological Physics and the State Health Departments of Illinois and Iowa, initiated the Midwest Environmental Health Study (*7*) to conduct an epidemiologic investigation of the human populations exposed to elevated levels of radium 226 in drinking water. This paper reports the findings of that study.

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Methods

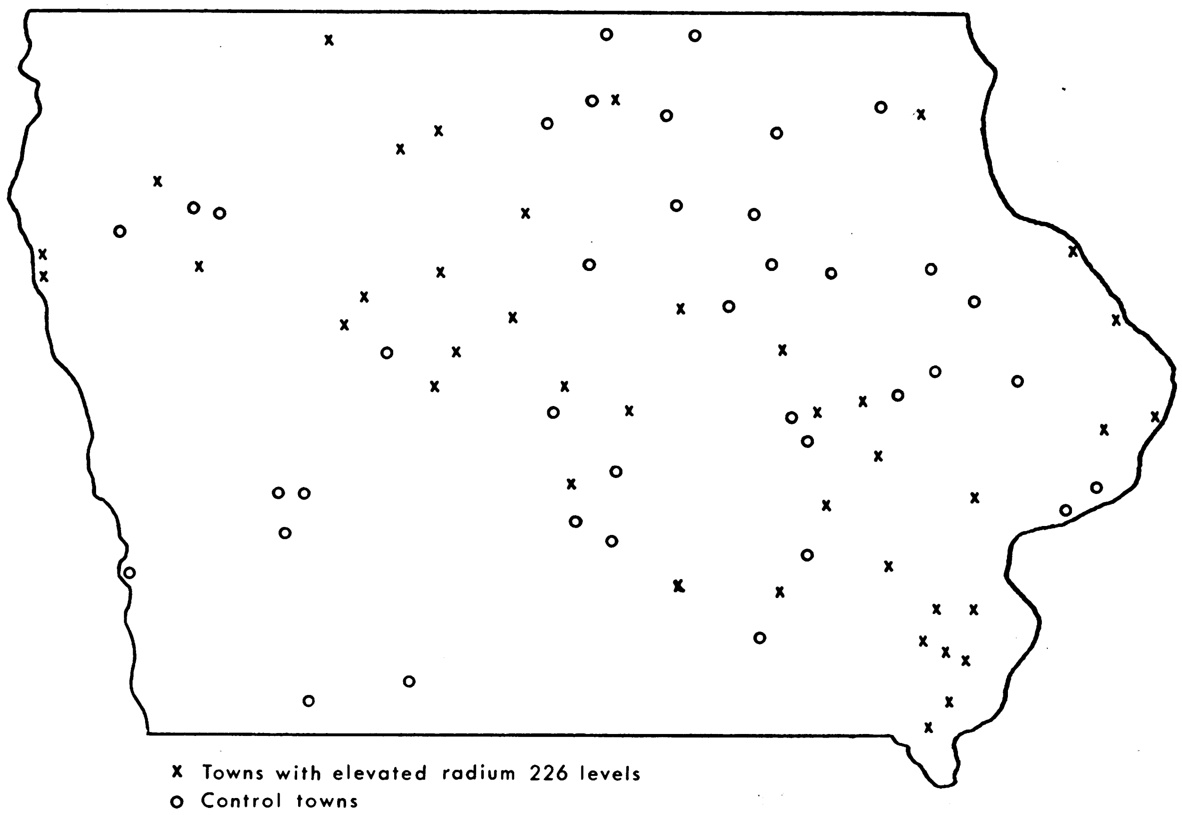
In 1962 the Public Health Service recommended that the radium 226 concentration in drinking water not exceed 3 pCi per liter (*8*). It has been shown (*9*) that regular, long-term ingestion of water containing 3 or more pCi radium 226 per liter is likely to result in a radium 226 whole-body burden at least twice that found in the population exposed only to normal levels of environmental radium 226 (*10*). For this study, elevated levels of radium 226 in water supplies were defined as those in excess of 3 pCi per liter.

The study was a descriptive epidemiologic approach to the question of whether human populations ingesting water containing elevated levels of radium 226 exhibit some biological effect at a rate greater than populations ingesting water containing negligible levels of radium 226. To help answer this question, comparable comprehensive programs of sampling and analysis identified municipal ground water supplies in both Illinois and Iowa containing 3 or more pCi radium 226 per liter at the time of sampling.

The investigation of possible biological effects in this study made use of certain mortality data collected from 1950 through 1962. Therefore, it was necessary to ascertain that the water supplies identified as having 3 or more pCi radium 226 per liter at the time of sampling were capable of having and likely to have had at least this level of radium 226 throughout the 13-year period of study. This was done by constructing an historical profile of each selected water supply. These profiles indicated any change in source wells, well depths, well construction, water treatment, and, wherever possible, the aquifer being used. Records of stable chemical analyses were used to determine source aquifers. On the combined basis of radiochemical analyses and historical profiles, 111 communities, 72 in Illinois and 39 in Iowa, were identified as probably having stable water supplies containing elevated levels of radium 226 throughout the study period. The historical profiles suggested that most of these communities also had elevated radium 226 levels in their water supplies for some time before the study period.

In each State control communities were matched with the communities having elevated radium 226 levels, to provide a population with no known exposure to elevated levels of radium 226 in water. The matching procedure included an alphabetical review of all communities in the State, beginning with the community to be matched, and accepting, as a control, the first community to meet the following criteria: (*a*) a public ground water supply having records indicating a radium 226 concentration less than 1 pCi per liter, (*b*) a 1960 census population within 10 percent of that of the community to be matched, (*c*) a 1950 census population within 10 percent of that of the community to be matched, and (*d*) in communities with more than 10,000 population, a median population age within 2 years of that of the community to be matched. In several instances it was necessary to match one of the larger communities with a community having a surface water supply containing a negligible radium 226 concen-

Figure 1. Location of Iowa study towns



tration. The locations of the communities selected for this study are shown in figures 1 and 2.

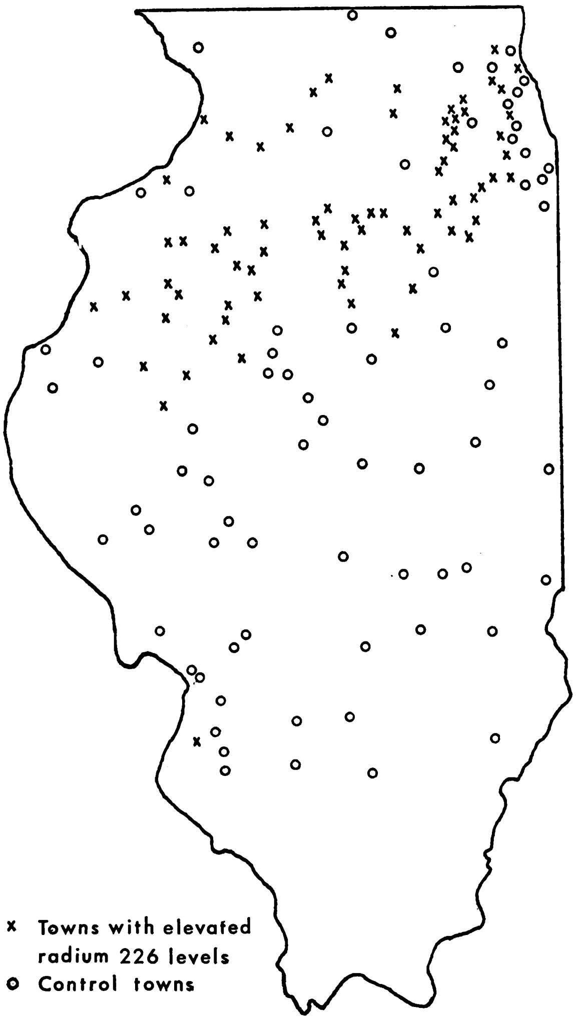
Based on the experience of persons having relatively large radium 226 body burdens and the fact that ingested radium concentrates in the skeleton, malignant neoplasm involving bone was considered one biological effect possibly related to radium 226 exposure. Deaths due in any way to malignant neoplasm involving bone are coded to category 196 of the International Classification of Diseases.

Accordingly, all death certificates coded to this category for residents of Illinois and Iowa during the years 1950 through 1962 were retrieved and copied for further analysis. An additional crude investigation of the possible health hazards associated with the ingestion of elevated radium 226 levels was made possible by tabulating deaths from all causes in 1959–61 occurring to residents of the selected study communities having populations greater than 10,000.

To calculate rates based on the period from 1950 through 1962, the population denominator was approximated for the various areas of interest as the average of the resident census populations in 1950 and 1960. The 1960 census figures were used as the denominator for the calculation of mortality rates based on the 1959–61 period. It was observed that communities with elevated radium 226 levels contained insignificant segments of nonwhite populations. Consequently, the need for adjustment for race was avoided by using only the white population for this study. Differences between calculated rates were tested for significance using a simple "two-tailed" test of differences in proportions based on the normal curve.

An effort was made to gain more specific information concerning such factors as the residence, occupation, and health patterns of persons having malignant neoplasm involving bone. Letters were written to physicians in Iowa and downstate Illinois (Illinois, excluding Chicago) requesting permission to interview patients known to have a malignant neoplasm involving bone. As a result of this request detailed histories were obtained for 36 patients in Iowa and 35 patients in Illinois. While the data from these histories did not lend themselves to rigorous analysis because of the bias inherent in the selection of patients by voluntary reporting, the information did confirm other observations concerning the mobility of the population and the uncertainty of diagnosis. Based on the 71 histories, no obvious common factors associated with place of residence, occupation, diet, family disease experience, medical or other therapy, or injury or other illness were recognized. In no instance was there a history of occupational or therapeutic exposure to radium.

Figure 2. Location of Illinois study towns



Results

Table 1 presents the distribution, by size, of the 111 communities in Illinois and Iowa identified as having water supplies containing elevated levels of radium 226. The weighted mean per capita exposure in the Iowa population was 3.4 pCi of radium 226 per liter and in Illinois 5.3 pCi per liter. The weighted mean figure for both States was 4.7 pCi of radium 226 per liter. The estimated mean per capita exposure in the control communities was well under 1 pCi of radium 226. In summary, this study observed a population that grew from 708,000 in 1950 to 908,000 in 1960 and was exposed to radium 226 levels in water at least 5 times those to which a control population was exposed.

The uncorrected annual mortality rate from malignant neoplasm involving bone during the 1950–62 period was 1.29 per 100,000 population for Illinois and Iowa. The U.S. rate was 1.19 during this period. The ratio of the mortality rate in females to the rate in males was 0.66 for Illinois and Iowa. The U.S. ratio was 0.69.

Table 2 presents adjusted mortality rates based on deaths coded to malignant neoplasm involving bone occurring to residents in the 111 study communities and in the control communities. The age-adjusted rates for both males and females were higher in communities with elevated radium 226 levels in water than in control communities, and the difference observed between the age-adjusted and sex-adjusted rates for the two exposure groups would be expected to occur by chance alone only 8 times in 100. Rates for these categories were also calculated using the native-born white population only. The removal of the foreign-born population lowered the observed rates because of the preponderance of foreign-born persons in the older age groups where mortality rates were highest.

Table 2. Mortality rates based on deaths coded to malignant neoplasm involving bone, white population, 1950–62

Sex	Number deaths		Death rates [1]		Probability factor
	Exposed group [2]	Control group	Exposed group [2]	Control group	
Male	83	68	1.65	1.33	0.18
Female	65	51	1.19	.96	.25
Total	148	119	1.41	1.14	.08

[1] Deaths per 100,000 per year. Rates for males and females are age adjusted and total rate is age and sex adjusted.

[2] Persons exposed to elevated levels of radium 226 in water supplies.

However, the relative differences between the exposed and control rates were only slightly changed from those in table 2.

Table 3 compares the age-specific mortality rates based on deaths coded to malignant neoplasm of bone in the two exposure groups. In six of the nine age groups the rates were higher in the population exposed to elevated radium 226 levels in water than in the control population. In the age groups 20–29 and 60–69 years the differences between rates were considered significant. Table 3 also demonstrates the bimodel age distribution of deaths coded to malignant neoplasm of bone described

Table 1. Distribution of population (1960 census) exposed to elevated levels of radium 226 in water supplies, by size of community

Community size	Illinois		Iowa		Illinois and Iowa			
					Towns		People	
	Towns	People	Towns	People	Number	Percent of total	Number	Percent of total
More than 10,000	16	454,100	5	238,400	21	19	692,500	76
2,500–10,000	20	105,600	7	37,500	27	24	143,100	16
Less than 2,500	36	42,800	27	29,200	63	57	72,000	8
Total	72	602,500	39	305,100	111	100	907,600	100

Table 3. Age-specific mortality rates based on deaths coded to malignant neoplasm involving bone, white population, 1950–62

Age group (years)	Number deaths: Exposed group [2]	Number deaths: Control group	Death rates [1]: Exposed group [2]	Death rates [1]: Control group	Probability factor
0–9	2	5	0. 10	0. 24	0. 26
10–19	14	8	. 93	. 53	. 20
20–29	9	2	. 68	. 14	. 03
30–39	5	5	. 35	. 33	. 92
40–49	7	11	. 53	. 80	. 40
50–59	18	22	1. 59	1. 88	. 60
60–69	37	22	4. 21	2. 59	. 07
70–79	39	30	7. 77	6. 15	. 33
80 and over	17	14	9. 24	8. 48	. 81

[1] Deaths per 100,000 per year.
[2] Persons exposed to elevated levels of radium 226 in water supplies.

in detail by Bugher and Mead (*11*). Age-sex-adjusted rates for the two segments of this curve, separated at age 30, were calculated. Mortality rates for both age groupings were higher in the population exposed to elevated levels of radium 226 than in the control population—the difference between rates was most significant in the population under 30 years of age ($P=0.10$).

An age-specific analysis of mortality from all causes of death in study communities of more than 10,000 population is presented in table 4. While the total age-sex-adjusted rates were comparable in the exposed and control groups, the age groups 0–9 and 30–39 years in the communities with elevated radium 226 levels exhibited significantly higher mortality rates than the same age groups in the matched control.

In tables 5 and 6 the mortality rates based on deaths coded to malignant neoplasm involving bone are presented separately for the two exposure groups in Illinois and Iowa. In both States and in both sexes the rates for the exposed populations were greater than the rates for the control populations. The adjusted rates are presented for the populations in downstate Illinois and in Iowa which were not included in either study group. These populations were exposed to mean radium 226 concentrations in water estimated to be intermediate to the concentrations in the exposed and control groups.

To determine whether the observed differences between the mortality rates in the two groups were consistent with respect to time, the age-sex-adjusted rates were compared for the periods January 1950 through June 1956 and July 1956 through December 1962. During both periods the rates were higher in the exposed population than in the control population, although the difference was relatively greater during 1950–56 than during 1956–62.

To investigate the possible effect of the terminology used by the certifying physician in stating the cause of death on the death certificate on the mortality rates derived from deaths coded to neoplasm of bone, the death certificates were analyzed in two terminology groups. One group consisted of certificates on which the term "sarcoma" appeared anywhere in the section reserved for stating the cause of death. The remainder of the certificates comprised the second group, which consisted primarily of certificates stating the term "carcinoma" involving

Table 4. Age-specific mortality rates based on deaths from all causes, white population, 1959–61

Age group (years)	Number deaths: Exposed group [2]	Number deaths: Control group	Death rates [1]: Exposed group [2]	Death rates [1]: Control group	Probability factor
0–9	1, 242	1, 149	3. 45	3. 16	0. 03
10–19	171	162	. 62	. 65	. 65
20–29	210	234	1. 05	1. 08	. 76
30–39	405	369	1. 83	1. 55	. 02
40–49	903	978	4. 26	4. 24	. 92
50–59	1, 920	1, 986	10. 3	10. 2	. 98
60–69	3, 684	3, 576	24. 4	24. 8	. 49
70–79	5, 142	4, 860	55. 4	56. 6	. 28
80 and over	4, 794	4, 281	145. 1	149. 9	. 12

[1] Deaths per 1,000 per year.
[2] Persons exposed to elevated levels of radium 226 in water supplies.

bone. In both groups the population exposed to elevated levels of radium 226 in water had a higher age-sex-adjusted rate than the control population. The relative difference in rates was greater for the "other" category than for the "sarcoma" category.

Discussion

Based on retrospective analysis and comparison of selected mortality rates in a population exposed to elevated levels of radium 226 in drinking water with those rates in a matched control population, three observations appear noteworthy:

1. The adjusted mortality rates based on deaths coded to malignant neoplasm involving bone were consistently and sometimes significantly higher in the exposed population than in the control, whether analyzed by age, sex, State of residence, nativity, time, or terminology describing the cause of death.
2. The populations in Iowa and downstate Illinois not included in the exposed or control groups, but exposed to radium 226 levels in drinking water ranging from 0 to 2.9 pCi per liter, exhibited adjusted bone neoplasm mortality rates higher than those in the control group and lower than those in the exposed group.
3. While the total adjusted mortality rates based on deaths from all causes in study towns with more than 10,000 population were not significantly different in the exposed and control groups, the exposed population in the age groups 0–9 and 30–39 years exhibited significantly higher rates than the control population in these age groups.

Significant differences in mortality rates based on deaths coded to malignant neoplasm involving bone have been noted between some population groups in the absence of a logical explanation based on exposure to radium 226 in drinking water. For instance, the adjusted bone neoplasm mortality rate in the Chicago population significantly exceeded the rate in the control population, even though Chicago is served by a surface water supply having only 0.03 pCi of radium 226 per liter. Similarly, Bugher and Mead (*11*) have demonstrated significant regional differences in bone neoplasm mortality rates that appear to be unrelated to environmental radium 226 exposure. The high rate in the Chicago population suggested the possibility that this effect was related to the degree of urbanization. However, this suggestion was not consistent with the finding that the adjusted bone neoplasm mortality rate in communities of more than 10,000 population, excluding Chicago, was identical to the rate for the remainder of the population; that is, those living in communities smaller than 10,000 or rural areas.

In the absence of an adequate understanding of the etiology of neoplasm involving bone, the differences noted in this study between exposed and control populations should not be discounted, particularly since they are in the direction suggested by radiation damage theory. However, the findings should be interpreted

Table 5. Mortality rates based on deaths coded to malignant neoplasm involving bone, white population in Illinois towns, 1950–62

Sex	Number of deaths			Death rate [1]			Probability factor [4]
	Exposed group [2]	Control group	Downstate Illinois [3]	Exposed group [2]	Control group	Downstate Illinois [3]	
Male	51	45	461	1.61	1.36	1.54	0.40
Female	44	35	293	1.26	1.04	1.01	.38
Total	95	80	754	1.43	1.20	1.27	.25

[1] Deaths per 100,000 per year. Rates for males and females are age adjusted and total rate is age and sex adjusted.
[2] Persons exposed to elevated levels of radium 226 in water supplies.
[3] Not included in either study group.
[4] Probability factor is for the comparison of exposed and control rates.

Table 6. Mortality rates based on deaths coded to malignant neoplasm involving bone, white population in Iowa towns, 1950–62

Sex	Number deaths			Death rate [1]			Probability factor [4]
	Exposed group [2]	Control group	Iowa [3]	Exposed group [2]	Control group	Iowa [3]	
Male	32	23	200	1. 74	1. 26	1. 46	0. 24
Female	21	16	126	1. 06	. 82	. 96	. 44
Total	53	39	326	1. 39	1. 03	1. 20	. 15

[1] Deaths per 100,000 per year. Rates for males and females are age adjusted and total rate is age and sex adjusted.
[2] Persons exposed to elevated levels of radium 226 in water supplies.
[3] Not included in either study group.
[4] Probability factor is for the comparison of exposed and control rates.

only with full knowledge of the limitations inherent in the methodology and sources of data that were used.

The denominators for the two study groups were selected retrospectively and their composition and size were determined by simply using 1950 and 1960 residence census data. By definition, the denominators were to be composed of persons exposed to either elevated levels of radium 226 in water or exposed to negligible levels of radium 226 in water. However, from a radiobiological standpoint, radiation exposure due to radium 226 results from a complex process involving ingestion, uptake, and skeletal deposition, all of which are influenced by time, age, and metabolism. While these factors can and have been investigated individually (*9*, *12*), the classification of all the residents of a community into a single exposure group for use as a denominator constituted an extremely crude approximation.

Data collected by A. D. Ball at the Iowa State Hygienic Laboratory during the course of this study indicated that within certain communities significant variations occurred in radium 226 water levels with time and by sampling location. These variations, coupled with the mobility characteristics of the population, can lead to markedly different exposures among persons from the same community. Similarly, the presence of other naturally occurring, bone-seeking radionuclides in a water supply or the widespread use of home water softeners which effectively remove radium from water could also be significant factors in the validity of a denominator population. Compounding the problem of relating exposure to effect is the possible existence of age-dependent radiosensitivity in man.

A crude estimate of the mobility characteristics of persons from Illinois and Iowa either suffering from or having died from a malignant neoplasm involving bone is presented in table 7. For the purposes of this estimate, the listing on a death certificate of place of birth and place of residence at death as being the same county constituted lifelong residence. The personal interviews, of course, provided more accurate data concerning this question. The average values from these sources of information sug-

Table 7. Estimate of percentage of lifelong white residents within a county based on the experience of persons suffering from or dead from malignant neoplasm involving bone in Illinois and Iowa, by age group and source of information

Age group (years)	Estimated percentage based on—			Overall average
	Death certificates		Personal interviews, Illinois and Iowa	
	Illinois	Iowa		
0–19	58	42	46	49
20–39	37	35	30	34
40–59	36	19	21	25
60–79	18	19	18	18
80 and over	12	7	18	12

gested that less than 20 percent of the population in the age groups exhibiting the highest mortality rates were lifelong residents of their place of residence at death. However, the effect of this apparent mobility of the population is somewhat tempered by the length of time spent at the last place of residence (table 8). The data in table 8 were derived from a representative sample of Illinois death certificates coded to bone neoplasms.

The numerators selected for the calculation of rates in this study suffered from the same deficiencies with regard to residence as did the denominators. The retrospective selection of the numerator from vital statistics data precluded the opportunity of obtaining for each individual death a history concerning environmental exposure to radium 226 as well as possible medical or occupational exposures to radium 226. This limitation was of particular concern because of the number of women in northern Illinois who were known to have worked in the radium dial painting industry (*13*).

However, there were indications that these occupationally exposed persons did not significantly affect the observed rates in the study population. Because the radium dial painters were women, an unequal distribution of their deaths in the exposed and control groups would have tended to produce a difference between the ratios of the female mortality rate to male mortality rate in the exposed and control groups. However, a ratio of 0.72 was found in both groups. Of the 1,876 death certificates from Illinois and Iowa coded to malignant neoplasm of bone, 3 mentioned an association with radium. Of these, one was for a resident of a control community and the remaining two were for persons not from study communities.

Table 8. Median residence time at last place of residence for 437 white persons with death coded to malignant neoplasm involving bone, Illinois, by age group

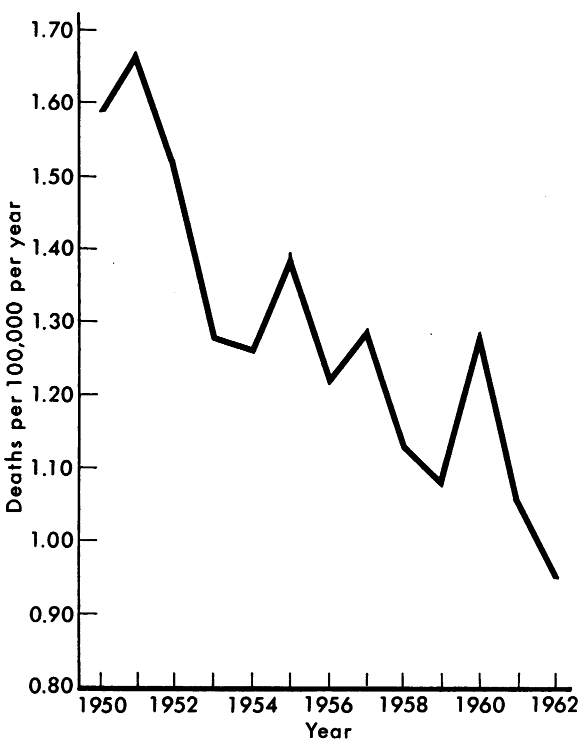
Age group (years)	Number persons	Median residence time (years)
0–19	91	11
20–39	54	11
40–59	101	30
60–79	101	42
80 and over	90	40

Another limitation of the vital statistics data was the lack of definition of the effect being measured, namely, death coded to malignant neoplasm involving bone. In addition to a study of deaths from all neoplasms involving bone, it would have been desirable to analyze only those deaths due to primary malignant bone neoplasm, since this is the type of neoplasm most commonly associated with a history of excessive radium 226 ingestion. However, Auerbach (*14*) has reported that only 35 percent of the death certificates in Illinois coded to malignant neoplasm involving bone are for primary malignant bone neoplasm. Dr. M. G. Sirken, National Center for Health Statistics, Public Health Service, referring to data from the same study in a 1964 personal communication, pointed out that deaths due to primary malignant bone neoplasm cannot be distinguished from deaths due to other bone malignancies on the basis of the entries made on death certificates by certifying physicians.

Table 9. Diagnostic terms appearing on death certificates coded to malignant neoplasm involving bone, 1950–62, by area

Area	Total certificates	Certificates using carcinoma or cancer		Certificates using sarcoma		Certificates using other terms	
		Number	Percent	Number	Percent	Number	Percent
Chicago	529	268	50. 7	237	44. 8	24	4. 5
Downstate Illinois	929	458	49. 3	424	45. 6	47	5. 1
Iowa	418	215	51. 4	177	42. 4	26	6. 2
Total	1, 876	941	50. 2	838	44. 6	97	5. 2

Figure 3. Crude mortality rates, by year, based on malignant neoplasm involving bone, white population in Illinois and Iowa



A comparison of the distribution by age at death and anatomical site of neoplasm on the death certificates used in this study with the distribution of these factors in 985 cases of primary malignant bone sarcoma reported by Coley (*15*) revealed marked discrepancies in both categories. This suggested, in agreement with Auerbach (*14*), that these death certificates included many deaths not due to primary malignant bone sarcoma. Similar findings in England, Wales, and Canada have been reported in detail by Mackenzie and associates (*16*) and Phillips (*17*).

Despite the lack of definition of the effect measured in this study, the death certificates exhibited remarkable consistency from area to area in the gross terminology used in stating the cause or contributing cause of death. To investigate the use of terminology by area, the death certificates were separated into three groups: (*a*) those using the term "sarcoma," (*b*) those using the term "carcinoma" or "cancer," and (*c*) "others." The percentage of the death certificates in each of these groups, by area, is shown in table 9.

A decline, with time, of mortality rates based on deaths coded to malignant neoplasm of bone has been reported in both the United States (*11*) and England and Wales (*16*). A similar decline was evident in Iowa and Illinois during 1950–62 (fig. 3). However, on closer inspection, the decline in Iowa and Illinois appeared to be restricted to the age groups 30 years and over, as shown in table 10. Since both Mackenzie (*16*) and Auerbach (*14*) have reported that primary malignant bone sarcoma is most accurately reported on death certificates in the younger age groups, this finding suggests that the primary malignancies are not declining and that the observed decline is due to a change in the accuracy of reporting in the older age groups.

Summary and Conclusions

An epidemiologic investigation of human populations exposed to elevated levels of radium 226 in drinking water identified 111 Iowa and Illinois communities, with a combined population of almost 1 million people, exposed to a mean drinking water concentration of 4.7 pCi radium 226 per liter during 1950–62.

Based on a retrospective analysis of data from death certificates, this population group exhibited an adjusted bone neoplasm mortality rate of 1.41 deaths per 100,000 compared with a rate of 1.14 in a control population (P=0.08). An intermediate rate of 1.25 was exhibited by the populations in downstate Illinois and Iowa,

Table 10. Crude mortality rates based on deaths coded to malignant neoplasm involving bone, white population in Illinois and Iowa, 1950–56 and 1957–62, by age group

Age group (years)	Number deaths		Death rates [1]		Probability factor
	1950–56	1957–62	1950–56	1957–62	
Under 30	159	141	0. 44	0. 42	0. 66
30 and over	928	648	2. 27	1. 77	. 01
Total	1, 087	789	1. 42	1. 13	. 01

[1] Deaths per 100,000 per year.

which were not included in either study group but exposed to an estimated radium 226 concentration higher than that in the control communities and lower than that in the exposed communities. The difference between the rates in the exposed and control groups was more significant in the population under 30 years of age than in the group 30 years and over. Some significant differences were noted between the bone neoplasm mortality rates of population groups with no apparent difference in radium 226 exposure.

In view of the limitations inherent in the retrospective approach delineated in this report, confirmation or refutation of the findings will require a prospective, analytic epidemiologic study. While theoretically possible, the feasibility of such a prospective study from a practical standpoint may be limited by the fixed size of the available exposed population. The necessary duration of a study in this population that would provide a statistically definitive result has been calculated. With the differences between exposed and control rates that can be expected, the most conservative figures exceed 20 years of observation in a population of this size. Therefore, it appears that the identification of additional exposed population groups would offer the greatest hope of a more meaningful study of this aspect of the problem.

A comparison of adjusted mortality rates from all causes of death in exposed and control communities with populations of more than 10,000 revealed no significant difference. However, the mortality rates in the exposed groups aged 0–9 and 30–39 years were significantly higher than in the control groups of these ages. This finding deserves further investigation with respect to the causes of death responsible for the apparent excess in mortality and the consistency of this difference in communities with populations of less than 10,000.

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