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Bone Sarcoma in Humans Induced by Radium: A Threshold Response?

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Abstract: The radium isotopes, ^{226}Ra and ^{228}Ra , have induced in humans, at sufficiently high levels in the body, malignancies in the skeleton, primarily bone sarcomas. They have also induced, at approximately half the frequency, carcinomas arising in the paranasal sinuses and mastoid air cells. There is no evidence that any leukemias have been induced by internally deposited radium, nor any other solid cancers. However, some radium cohorts have shown elevated levels of breast cancer, while others have not. It has been suggested, at least for the dial painter population, that breast cancer may be the consequence of external radiation from the radium dial paint.

Prior to the termination of the U.S. radium studies program in 1990, a concerted effort was made to verify, for each of the measured radium cases, the published values of the skeletal dose and the initial intake of radium. These were derived from body content measurements made, on the average, some 40 years after radium intake. Corrections to the assumed radium retention function resulted in a considerable number of dose changes. These changes, in turn, have changed the shape of the dose response function. It now appears that the induction of bone sarcomas is a threshold process; below the calculated threshold no malignancies have been seen, above the level the probability of the induction of a malignancy increases rapidly.

1. INTRODUCTION

Some thirty years ago Evans [1] proposed that a Practical Threshold existed for the induction of malignancies in humans by internally deposited radium. A review of the data that has accumulated since he made that proposal suggests a somewhat different interpretation for the bone sarcoma incidence in the now considerably enlarged population of radium cases.

What did Evans mean by a Practical Threshold? In the abstract of a 1967 publication [2] he stated:

"When the cumulative skeletal dose in rads decreases, the tumor appearance time for the sarcomas and carcinomas associated with skeletal deposits of Ra or MsTh appears to increase. This leads to the identification of a "practical threshold" of dosage, below which the required tumor appearance time generally exceeds the life-span, and hence radiation-induced tumors appear with negligible frequency."

Today the accumulated data suggests that Evans was not entirely correct, there is not a Practical Threshold for the induction of bone tumors in the human $^{226}/^{228}\text{Ra}$ cases. Instead there appears to be a real threshold, a dose below which such malignancies have not been seen. Evans suggested a practical threshold existed at a skeletal dose of 10 Gy (1000 rads) [2]. When Evans made these statements he was studying the results made from about 450 cases, who had obtained their radium in a variety of ways. Of these, he concentrated on a group of 173 epidemiologically suitable cases

who experienced 26 bone sarcomas and 9 head-cavity carcinomas. Today we have a population of 2383 cases for whom we have reliable body content measurements; they experienced 64 bone sarcomas, none below 10 Gy. From this population we can draw a cohort with similar age, sex, method of exposure and period of exposure, the female dial workers. Further, we now limit the analysis to one malignancy, the bone sarcomas, instead of the two types of malignancies. This cohort of 1530 women experienced 46 bone sarcomas.

2. THE BONE SARCOMAS

The data that has been accumulated on these U.S. radium dial workers is unique in many aspects. The following points are relevant to the analysis of bone sarcoma incidence.

- These women were exposed to radium in the dial industry between 1913 and 1950. Those exposed after 1950 have not been included in this cohort.
- Their body content of radium was measured long after their exposure; the average time was 40 years after starting in the dial industry.
- From the measured radium body content the original intake of radium was calculated by means of an assumed radium retention function.
- The skeletal dose was calculated from the original intake and summed over the interval from exposure to diagnosis of a sarcoma, or death, or 1990 for those still living. The assumed retention function was a critical factor in this summation.
- Due to the long half-life of ^{226}Ra , and the slow release of radium from the skeleton, the irradiation of the skeleton continued throughout the life of the contaminated individual.
- The skeletal doses in this radium population range over almost five decades of dose.

In the late 1980s sufficient evidence had accumulated to show that, as previously demonstrated in studies with dogs [3], radium retention in humans was dose dependent [4, 5]. High dose cases retained radium more tenaciously than lower dose cases. This led to a complete recalculation of the initial intakes and skeletal doses, making use of the ICRP 20 retention function for radium [6, 7], modified for the effect of the radium intake level. It is with these revised radium doses that the evidence for a bone sarcoma threshold becomes evident.

The time from first exposure to radium to the time of sarcoma diagnosis is plotted against the skeletal dose for each of the 46 bone sarcoma cases in Fig. 1. Also shown on this plot are the cumulative doses for remainder of the 1530 dial workers in the cohort, indicated by the number placed in each decade of dose.

It is evident that no sarcomas appeared in the 1370 dial workers who accumulated less than 10 Gy to the skeleton. Had we performed this analysis on the total number of measured radium cases, 2383, the general appearance would have been the same. All 64 bone sarcoma cases occurred in the 264 cases with more than 10 Gy, while no sarcomas appeared in the 2119 radium cases with less than 10 Gy.

Dose response functions may be calculated for this cohort of female radium dial workers. Previous analyses of these radium cases used numerical fits to a general dose-response function that related the probability of the induction of a bone sarcoma to the magnitude of the radium insult. The functions tested have been continuous functions that passed through the origin (zero probability at zero dose) and included the full range of measured skeletal doses. Dose response functions of the form

$$\text{Incidence} = a D^2 e^{-b D}$$

have been proposed in previous reports [8, 9]. Such functions describe the data well and were proposed as reliable predictors of future radium-induced bone sarcomas. Here Incidence was in

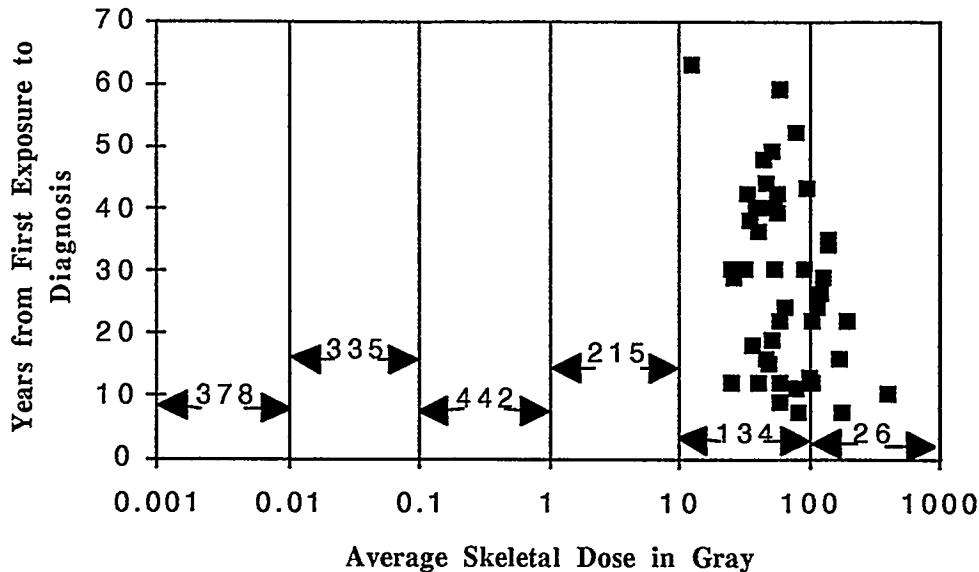


Figure 1. The 46 bone sarcomas in the cohort of 1530 female dial workers are plotted as black squares, indicating their appearance time and dose for each sarcoma case. The total number of cases in each decade of dose are also indicated.

units of sarcomas per person year at risk, D was in units of skeletal dose or units of systemic intake, and a and b were constants determined by the fitting procedure.

The most recent presentation [10], in contrast, postulated that a threshold might exist for radium-induced bone sarcomas. It suggested that there was zero risk up to a threshold dose, above which the risk increased at a rapid rate. It was shown that a continuous dose response function that passed through the origin for bone sarcomas could only be fit to the data with an expression of the form

$$\text{Incidence} = a D^{\text{exponent}} e^{-b D}.$$

Here the numerical value of the exponent had to be in the range 2.7 to 4.1, with the value 3.15 for the exponent appearing to be the best fit to the data. Needless to say, it is difficult to find any physical meaning for such a dose response function.

It appears that instead of a continuous function from the zero-zero point up to the observed data points, a pair of functions should be considered, with zero incidence up to a threshold value, and a steeply rising curve above that point. This published analysis [10] used systemic intake as the measure of radium risk. Systemic intake, the quantity of radium that entered the blood during the period of exposure to radium, has been a useful parameter. It is time invariant, in contrast to skeletal dose, which increases as long as the radium-exposed subject lives. The U.S. radium cases were long-lived; approximately 1000 were still living when the study was terminated in 1990. It correlates quite well with skeletal dose, as is shown in Fig. 2, where log skeletal dose in gray is plotted against intake in log kilobecquerels.

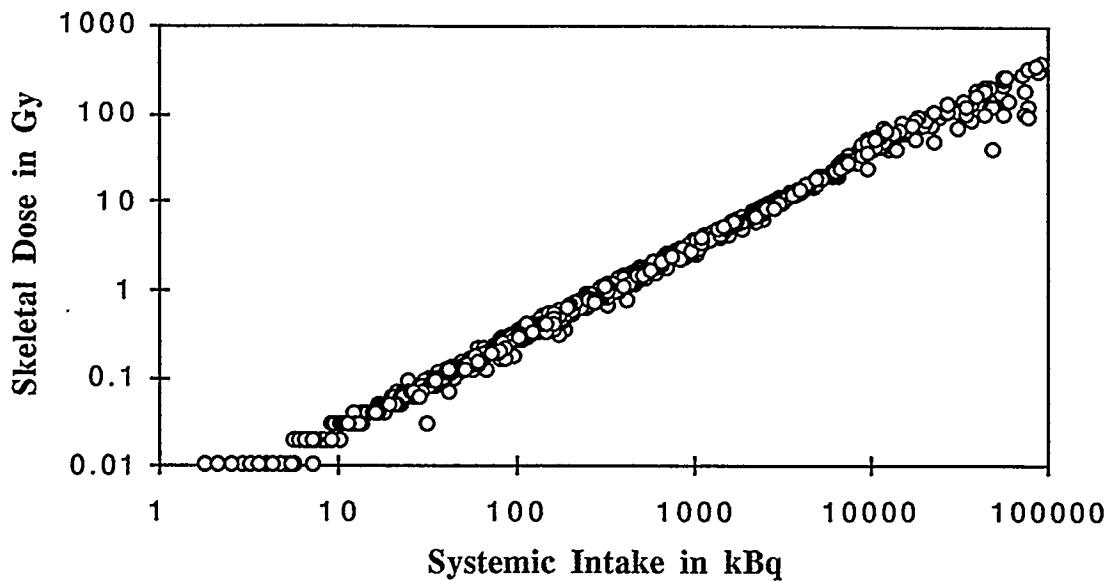


Figure 2. Each of the 1530 female workers is plotted to show the relation between their systemic intake and their skeletal dose. The correlation coefficient for dose in gray and intake in kBq is 0.93.

In the above referenced publication [10] the threshold for bone sarcoma was found to be 2924 kBq. From the relationship between systemic intake and skeletal dose shown above, this translates into a skeletal dose threshold of 7.5 Gy.

Alternatively, the female dial cohort can be divided into dose groups and fitted to a dose response function directly. Table 1 shows the dose distribution of the 1530 dial workers and their bone sarcomas.

TABLE 1. DISTRIBUTION BY DOSE OF 1530 MEASURED RADIUM CASES

Dose Range Gy	Weighted Dose Gy	Cases	Sarcomas	Person Years at Risk	Incidence: Sarcomas/ Person Yr
>100	156.78	26	13	494	0.0263
≥50.0 < 100	62.72	38	17	1,176	0.0145
≥25.0 < 50.0	37.19	47	15	1,937	0.0077
≥10.0 < 25.0	15.92	49	1	2,537	0.0004
≥5.00 < 10.0	7.046	52	0	2,918	0
≥2.50 < 5.00	3.520	57	0	3,162	0
≥1.00 < 2.50	1.584	106	0	5,856	0
≥0.50 < 1.00	0.705	96	0	5,015	0
≥0.25 < 0.50	0.352	141	0	7,103	0
≥0.10 < 0.25	0.156	205	0	9,422	0
≥0.05 < 0.10	0.067	167	0	7,314	0
≥0.025 < 0.05	0.035	80	0	3,419	0
< 0.025	466	0	0	21,748	0

Several different continuous functions can be fit to this data. One of the best fits is given by

$$\text{Incidence} = A \times (D^X) \times e^{(-B \times D)}$$

$$\text{where } A = 1.53 \times 10^{-6}$$

$$B = 1.84 \times 10^{-2}$$

$$X = 2.5$$

and D = Dose in gray

with a χ^2 probability of $p = 0.31$.

Several other values of the exponent on the dose will also give acceptable fits for such continuous functions that pass through the origin.

When these dose groups are plotted in Fig. 3 the evidence for a threshold is marked. Dividing the dose groups up in this manner suggests that a threshold exists in the neighborhood of 10 Gy.

Functions of the form

$$\text{Incidence} = \text{Constant} + A \times (D^B)$$

and

$$\text{Incidence} = \text{Constant} + A \times (D^{(\text{a specified exponent})}) \times e^{(-B \times D)}$$

were fit to the data, and some acceptable fits were found. These allow the constant term to define the threshold value when the Incidence equals zero, but all have a non-integer exponents on the dose term. The best fit was

$$\text{Incidence} = -3.201 \times 10^{-2} + 1.575 \times 10^{-2} \times D^{0.259}$$

which yields a threshold at 15.4 Gy

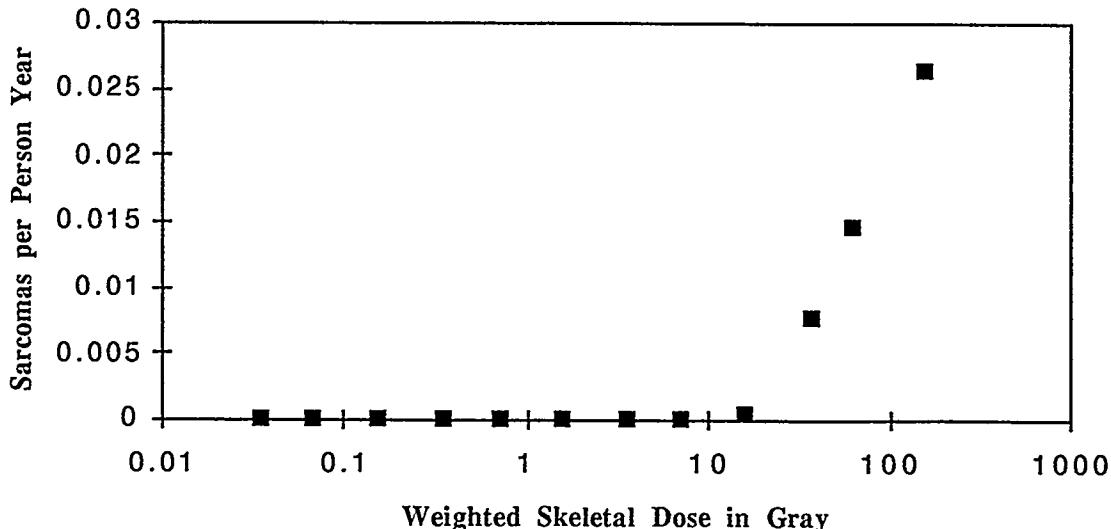


Figure 3. The solid points show the sarcoma incidence in each of the 12 dose groups from Table 1.

One should be aware that changing the size of the dose groups can have a marked effect on the shape of the dose response plot. It is not my purpose to specify precisely where the threshold is, it is only to point out that this data set strongly suggests that there is a threshold. Indeed, it would be very difficult to determine precisely the location of a threshold, if one exists.

3. THE HEAD CARCINOMAS

In addition to the bone sarcomas, radium deposition in humans is known to be responsible for the induction of head carcinomas, carcinomas that arise in the paranasal sinuses or mastoid air cells. These malignancies take longer to appear than the bone sarcomas, the earliest appearance time was 19 years after first exposure to radium, in contrast to only 5 years for the sarcomas. Both appear at very long times after exposure, as late as 63 years. There have been only half as many of the head carcinomas as bone sarcomas. In the total measured population, there were 32 carcinomas to 64 sarcomas; in the dial worker cohort the ratio was 19 to 46. As a consequence of the small number of the head carcinomas, there is insufficient statistical power to differentiate between alternate forms of dose response functions. It probably would be appropriate to calculate the risk of bone sarcoma for a given radium exposure, then reduce this risk by half to predict head carcinoma risk for a given exposure.

These radium induced malignancies have occurred more often in women than in men, in large part due to the much greater number of women employed in the dial painting industries. However, there were many males who received high levels of radium from medical treatments or exposure in chemical plants. When the dose response relation for bone sarcomas derived from female dial workers is applied to this population, it predicts significantly more sarcomas than were observed [11]. This suggests, but does not prove, that males may be less likely than females to develop bone sarcomas from internally deposited radium.

Before leaving the subject of radium-induced malignancies, it should be noted that no one who entered the dial painting industry after 1925 has developed either of the radium induced tumors. It was in 1925 that the request was made that dial painters were not to tip their brushes with their mouths. The dial painting studios had no rules for cleanliness, no attempts were made to clean up the spilled radium, and of course there were no health physicists monitoring their activities in those days. However, just the simple instruction, "Don't put the brush in your mouth" was sufficient to stop completely the induction of malignancies.

Note, however, that this did not put an end to the use of radium for intravenous injections as a medication or its use as an additive for bottled drinking waters. These sources of internal radium deposition continued to exist, and accounted for the induction of radium-induced malignancies in additional persons exposed after 1925.

4. OTHER MALIGNANCIES

Radium-induced leukemias have always been an expected consequence of radium deposition in bone. However, they have not been seen in excess of expected numbers in any cohort of radium cases [12].

Two other malignancies have been at times associated with internal radium, multiple myeloma and female breast cancer. The number of multiple myeloma cases is too small for any decision to be reached at this time. In regard to the breast cancers, the numbers are larger, but the studies are confounded by uncertainties. For example, dial painters as some sites had clear excesses of breast cancer, while at other sites the numbers observed were considerably lower than expected. In addition it has been recognized that external radiation to the breast tissue from the radium in the paint being used could have delivered a significant dose to the breast tissues, and thus might be the cause of some of the breast malignancies.

5. LIFE SHORTENING

The measurement of life shortening among the female dial workers should be mentioned in this summary. In two studies [13, 14] it has been shown that the malignancies induced by radium, the

bone sarcomas and the head carcinomas, are the only causes of life shortening. Stehney et al. [13] summarized their findings as follows:

"This study has demonstrated that when the radium tumor deaths are removed, the average survival of the dial worker population is indistinguishable from estimates of the survival of contemporary white females of the same age. This is a remarkable result, for it implies that, to the precision obtainable with a population of some 1000 persons, the life expectancy of the remaining population was unaffected by radium burden."

6. CONCLUSIONS

The study of the U.S. radium cases has been terminated, and it is unlikely that it could or would be reinstated before the majority of the still-living cases will have died. Thus the data that now exists are all that will ever be available in the future. No data is being collected at this time, nor is anyone funded to examine the existing patient files. It is the hope of those of us who have been involved in the collection of the radium records that the knowledge gained, imperfect as it is, will at least become part of the basic knowledge of the field of radiation research. Toward this end, the Department of Energy has funded the publication of a book that summarizes primarily the work on radium at the Argonne National Laboratory. However, it also includes a brief review of earlier studies in the U.S., particularly of the dial painters, and also describes some of the early medical uses of radium [15]. I would hope copies of this volume could be made available in the libraries of major research laboratories and universities.

It is appropriate to conclude with a quotation from the author's preface to this book.

"Given the number of people who acquired radium internally, it is remarkable how few suffered significant damage. To be sure, those who eventually developed radium-induced malignancies suffered severely. Those who acquired very large internal quantities of radium, as did many of the early dial painters, also suffered from what we today suspect were acute radiation doses leading to early deaths. However, the great majority of exposed individuals went through life with no recognizable consequences of their exposures. They lived as long as, and apparently in as good health as, their unexposed neighbors. This fact seems to have been little appreciated and seldom mentioned, but it may be the most important finding of the entire study".

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