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THE DETERMINANTS OF TIMES OF APPEARANCE OF RADIUM-INDUCED OSTEOSARCOMAS IN HUMANS: AGE AT APPEARANCE AND DOSE

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ABSTRACT

Determinants of time-until-tumor for osteosarcoma in U.S. radium cases have been reevaluated. Classically, a minimum induction period (latency period) of about five years has been recognized, but not an expression period. Lack of long induction periods at high doses has been ascribed to scarcity of subjects at risk. Recent experiments have suggested that induction periods are directly lengthened as doses decrease. Reanalyses of time-until-tumor data for 57 measured female osteosarcoma cases exposed to ^{226}Ra and/or ^{228}Ra support new interpretations: time-until-tumor for osteosarcomas is best described by age at tumor appearance, not by induction period; age at diagnosis increases as estimated initial radium intake decreases; and, there exists an expression period which can be truncated at the low end by the minimum induction period (or by age at exposure). The downturn in sarcoma incidence at very high doses is describable as the truncation of the expression period on its early side by the minimum induction period. These results depend strongly on the assumption of homogeneity of time-until-tumor processes in dial workers and in iatrogenic radium exposure cases.

Introduction

The "latency period" has been assumed to appropriately describe time-until-tumor relationships for radium-induced osteogenic sarcomas (1,2). However, in this paper we present evidence that age at expression (hereafter, age at diagnosis) is a more important parameter, perhaps the only important time parameter, when the radium-226 and -228 body burdens are acquired in adolescence

and early to mid-adult life.

This conclusion rests on analyses of all female osteogenic sarcoma cases with measured radium body burdens in the radium exposure registry at the Center for Human Radiobiology, Argonne National Laboratory. Our conclusion rests upon the combining of sarcomas from both the radium dial workers and from the iatrogenic radium exposure cases. This paper is preliminary in the sense that it emphasizes qualitative conclusions. Appropriate procedures for estimation of regression slopes are being investigated.

As pointed out by Raabe et al. (1), the relationship of dose to time-until-tumor has important risk assessment implications, as the expected time of occurrence may lie beyond the life expectancy. Substitution of age for latency period in this relationship does not negate the risk assessment implications he has perceived, but has added the complication of an increasing practical susceptibility at older ages.

Methods

The 57 women with both bone sarcomas and known radium body content (3) formed this preliminary study group. These included 42 dial workers (all dial painters), and 15 iatrogenic radium exposure cases. These latter included four radium water, one Radithor, and ten radium injection cases. The 57 cases are 72% of all known bone sarcomas in females in the study populations. The great majority of the unmeasured sarcoma cases were early cases, only three occurring after 1950.

Radium-226 body burdens have been measured primarily in vivo (35 cases); some have been measured from specimens obtained from living subjects and/or major portions of skeletons, cremation ash, or other specimens obtained after death. Details of measurement techniques and individual measurement data have been published (4). "Initial systemic intakes" were calculated by extrapolating ^{226}Ra

body contents at measurement back to time of exposure using the retention function of Norris et al. (5). ^{228}Ra burdens could frequently not be measured directly, but were estimated from knowledge of $^{228}Ra/^{226}Ra$ ratios in coworkers and/or in paint materials (4). Since we are dealing here with osteosarcoma, we use primarily the weighted function $^{226}Ra + 2.5 \times {}^{228}Ra$ presented by Rowland et al. (6) as our dose parameter. We investigate the effect of higher mesothorium levels in our analyses however, dichotomizing sarcoma cases on the $^{228}Ra/^{226}Ra$ ratio ($^{228}Ra/^{226}Ra \geq 0.5$, or $(^{226}Ra + 2.5\ ^{228}Ra)/(^{226}Ra + {}^{228}Ra) \geq 1.5$)). The induction period presented has been defined from initiation of employment: this yields correlations marginally superior to those where latency is defined from middle or end of the employment period.

Table 1 describes some characteristics of the cases. The dial painters were approximately 12 years younger than the iatrogenic cases. First exposures were nearly all in the 1920's, ranging from 1915 to 1931. Exposures of the iatrogenic cases occurred on the average about 5 years later, and occurred through 1931 while all dial workers with sarcomas had begun employment before 1926. At exposure the iatrogenic cases were 17.6 years older on the average than were the dial workers, and showed a wider range of ages at exposure.

Table 2 gives ages at diagnosis, induction periods, systemic radium intakes, and $^{228}Ra/^{226}Ra$ ratios for the two groups. As expected, the iatrogenic cases were diagnosed at a more advanced age. The mean induction periods, however, hardly differ (1 year) between the two groups, although the radium intakes of the iatrogenic cases average about one-third the intakes of the dial worker cases. High mesothorium intakes were frequent in the dial workers, but there were essentially no mesothorium exposures to the iatrogenic cases.

Statistical methods. Standard simple and multiple regression and correlation procedures were used, including the non-parametric Spearman correlations.

Exploratory analyses were carried out on the following variables: age and year of exposure, age and year at diagnosis, year of death, induction period, the logarithms of radium intakes (both with mesothorium given a weight of 1.0 and a weight of 2.5), the $^{228}Ra/^{226}Ra$ ratio, and the doses squared.

Only the osteosarcoma cases were analyzed, with age at diagnosis or induction period as the dependent variables. A more complicated modeling process treating dose- and time-specific osteosarcoma rates as functions of intake dose, the time parameters, and the interactions of the dose and time parameters is underway.

As shown in Table 3, nearly all possible follow-up on all study subjects with >50 μCi radium intake is in the past. Only 5% of possible person-years remain. Further, the last sarcoma in this series occurred in 1977, the second last in 1972. A case has occurred in 1982; it is not incorporated in the regressions but is presented later. Thus, few observations are being lost by censoring due to incomplete follow-up.

The regressions should be interpreted cautiously, however: while they reflect the observed distributions of events, given observed exposure and mortality patterns, the observations are censored in several practical ways which influence slope estimates, standard errors of estimate, and the distribution of residuals. A practical minimum induction period of six years exists: cases which would be predicted in a shorter interval do not occur. Secondly, few very high dose cases survived long enough to yield cases at older ages and high doses (>500 μCi intake). Thirdly, mortality from other causes censors the distribution of sarcoma cases at high ages in the low dose category. Only in the low-time, low-dose area is the distribution of sarcomas not censored (other than by the minimum induction period).

Results

Figure 1 shows a plot of induction period against dose for dial workers and iatrogenic cases. Except for censoring on the upper right (late ages, high doses), a reasonably rectangular distribution of onset dates appears. The iatrogenic cases do not appear to differ from the dial worker cases except by dose. The correlation is given by the r^2 of .18.

A similar plot, except exchanging age at diagnosis for induction period, is shown in Figure 2. The r^2, .33, is higher and the plot itself shows a strong correlation. The iatrogenic cases now clearly dominate the low dose, old age portion of the plot.

Table 4 gives both the Pearson and Spearman correlation coefficients between systemic radium intakes and ages at diagnosis and induction periods. For the group as a whole the correlation of age at diagnosis with dose is much stronger than that of induction period with dose. This finding does depend on combining the iatrogenic and dial painter cases, the dial workers alone yielding somewhat inconsistent results. However, there was very little variance in age at exposure among the dial workers, so that the ability to discriminate between induction period (age at diagnosis minus age at exposure) and age at diagnosis is very poor.

Dose parameter alternatives. The dose parameter $\log_{10}$ (^{226}Ra + ^{228}Ra) was compared with $\log_{10}$ (^{226}Ra + 2.5 ^{228}Ra) in the correlation analysis. Correlations were consistently superior for the Pearson correlations weighting ^{228}Ra more heavily: with age at diagnosis r^2 = .33, versus r^2 = .22; and with induction period r^2 = .18 versus r^2 = .16. Nearly identical findings obtained for the dial worker group alone and for the Spearman correlations.

The alternatives of using the dose square term, ($\log_{10}$ (^{226}Ra + 2.5 ^{228}Ra))^2, and the linear and square terms combined were investigated. In correlations with age at diagnosis, the dose square term alone yields an increase of less than 1% in

percent variance explained over the linear term, not sufficient to justify its use. For the addition of the squared to the linear term, the F ratio is only 0.43. In correlations with the induction periods, the dose squared term does contribute significantly to prediction: however, the total r^2, .25, still does not equal the r^2, .34, for the correlation of age at diagnosis with the two dose terms. When the iatrogenic and dial work cases are analysed separately, the same results are obtained.

Effects of the iatrogenic cases. For investigation of the marginal effects of the iatrogenic cases upon the regression coefficients, a dummy variable was defined for iatrogenic case status (= 1 if an iatrogenic case, 0 otherwise). Interactions of this dummy variable with the log dose and dose squared terms were also defined.

Each dummy variable term or interaction was statistically significant taken singly, and each yielded approximately equal r^2's. Neither the dose squared nor the linear dose interaction terms added significantly to the constant difference associated with iatrogenic case status ($F = 6.64$, $p = .0128$). Table 5 presents the regression equations for both the constant and the dose dependent difference, along with the regression for the exposure types combined.

As Figure 2 shows graphically, iatrogenic case status is strongly correlated with dose, and the variability in dose within either case group taken separately is sufficiently restricted to make estimation of within-group slopes unreliable.

This significant (positive) difference associated with iatrogenic case status has several possible interpretations. It may represent a remaining contribution of induction period, a truncation at the lower limit by age at exposure (plus minimum induction period), or may be an artifact resulting from the strong collinearity of iatrogenic case status with dose, implying a larger bone dose difference than given by our dose estimates.

Effects of mesothorium

As shown in Figure 3, a high proportion of the dial work cases had significant mesothorium (^{228}Ra) exposure, and these are concentrated at the high dose end. A mixture of ^{226}Ra and ^{228}Ra cases does appear, however, in the mid-dose range, and the plot in Figure 3 does not suggest heterogeneity of regressions between the two groups of cases.

The visual impression is supported by results of the regression analyses. A categorical exposure variable was defined corresponding to a ^{228}Ra intake greater than 50% of the ^{226}Ra intake; this variable and its interaction with log dose were included in regression equations of age at diagnosis and induction period versus log dose. None were statistically significant: f ratios for these marginal constant and linear trend terms were 2.26 and 2.13 ($p = .14$ and $p = .15$), and the contributions were not additive. In regressions with induction periods as the dependent variable, the mesothorium exposure variables were even less important than for age at diagnosis. Thus the mesothorium component of radium exposure has not affected time-to-tumor relationships in a way not already accounted for by the 2.5x weighting of ^{228}Ra in the overall dose.

Discussion

No clear pattern of increasing latent period with decreasing dose has previously been reported for the U.S. radium dial workers (2,7). This in itself has not been surprising as cancer latency periods in man have been frequently not been demonstrably related to intensity of exposure to the causal agent (8). There has been, however, good experimental evidence that latency periods for bone tumors are increased as radium burdens are decreased in both dogs and mice (1). (But latency period and age at tumor appearance cannot be distinguished when

animals are exposed at a uniform age.)

An increase in sensitivity to bone sarcoma induction with increasing age (within the age range encompassed by the data) could explain the findings presented above. The resulting closer correlation with age at appearance then becomes an artifactual finding. This explanation is consistent with the literature on soft-tissue sarcoma induction by chemical carcinogens. A recent review (9) of the modifying effect of aging on chemical carcinogenesis concludes that, with respect to sarcomagenesis following local exposure to polycyclic aromatic hydrocarbons, aging had a distinct stimulating effect which manifested itself by shorter latency or by an increase in tumor frequency or size. The same phenomenon was incidently observed for sarcomas in a study designed to determine effects of aging on development of epithelial tumors due to benzpyrene exposure (10).

In the radiobiology literature there does exist some evidence of age effects on osteosarcoma induction by internal emitters. Nilsson (11) suggests that puberty is the period of peak susceptability for osteosarcoma induction by ^{90}Sr in mice. His data suggest age effects on time-to-tumor relationships, and that these effects may be different at very high doses (0.4 and 0.8 μCi per gram body weight). Only in the lower, but still high, dose group of 0.2 μCi per gram body weight is the pattern consistent with these findings.

Momeni (12) studied skeletal injury in ^{226}Ra injected beagles, and demonstrated that the maximum rate of radiation induced skeletal change occurred at progressively older ages at lower injected activity levels. In only the high dose group (10 μCi/Kg body weight) were two age groups (first injections at 2-4 months and 14 months) studied. Latency to the point of maximum rate of change from mid-injection period was greatly reduced in the older group (180 days) compared to the young group (365 days). Corresponding ages were 650 and 500

days.

Gössner (13) has emphasized the role of biological factors on osteosarcoma risk from short-lived alpha emitters. He compared cumulative incidence of osteosarcomas in mice injected with 5 μCi/kg ^{227}Th at 1 and 6 months of age. The time to 50% incidence was 373 days for the younger group, 332 days for the older. Gössner plotted the ages at osteosarcoma in these groups and in a (much larger) control group, and found that the median age at onset of sarcoma was similar in the three groups. His conclusion was that "in experiments with low and even medium osteosarcoma risk the time of appearance of the tumours is mainly determined by the age of the animals. Therefore one could postulate an age dependent intrinsic factor which might influence the latency time of radiation-induced as well as spontaneous osteosarcoma."

This is the crucial issue: whether the age of the animal at exposure determines the induction period, or whether the age of the animal, post-exposure, controls the probability of expresion, or both. The former possibility is in accord with the literature on soft-tissue sarcomas, and could explain the data we have presented.

We lean toward the view that the age of the organism, post-exposure, does affect the probability of tumor expression, and thus the latent period, while not excluding an age effect upon sensitivity to induction. In our Figures 1 and 2, age at onset is clearly the best empirical predictor of time-of-onset in humans exposed in late adolescence and adult life. We have reanalysed the data of Mays and Speiss (14) and find that in their data age is also the best predictor of time of onset, except that subjects under the age of 16 are more sensitive and show a different slope than the older subjects. Gössner's mice data (13) supports this notion, as does one (10) of two (10,15) papers on soft-tissue sarcoma induction in mice.

If one tentatively assumes this view, it has some important implications for theories of sarcomogenesis. It would have fewer implications for Raabe's (1) time-to-tumor analyses: the practical threshold due to dose dependence of time remains.

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Table 1. Osteogenic sarcoma cases among measured female radium subjects.

Exposure groups	N	Birth year Mean	Year of first exposure Mean	Year of first exposure Range	Age at first exposure Mean	Age at first exposure Range
All sarcomas	57	1899.0	1921.6	1915-1931	22.4	13-55
Dial painters	42	1902.3	1920.3	1916-1925	17.8	13-31
Iatrogenic cases	15	1889.8	1925.3	1915-1931	35.4	13-55

Table 2. Mean systemic radium intakes, induction periods, and ages at diagnoses for measured female osteogenic sarcoma cases.

Exposure group	Age at diagnosis	Induction period	Systemic radium intake: Geometric mean[a]	$^{228}Ra/^{226}Ra$ ratio: Mean	$^{228}Ra/^{226}Ra$ ratio: Median
All sarcomas	50.2	27.8	765	1.9	0.2
Dial painters	45.3	27.5	1014	2.6	1.0
Iatrogenic cases	63.9	28.5	347	.03	0.0

[a] $^{226}Ra + 2.5 \times {}^{228}Ra$.

Table 3. Person-years from first exposure to radium-induced sarcoma, death, or last contact for study subjects with > 50 μCi initial radium intake.

	Systemic radium intake						
	<100	100-249	250-499	500-999	1000-2499	>2500	Total
Person-years of follow-up	1547	2301	2036	1134	928	343	8289
Person-years remaining[a]	137	165	99	21	8	0	430
Percentage of person-years observed	92	93	95	98	99	100	95

[a]Sum of individual life expectancies at age of last contact, from

Table 4. R^2's for Pearson and Spearman correlations of the logarithms of systemic radium intakes to induction periods and ages at diagnosis.

Systemic radium intake with:	All sarcomas		Dial painters		Iatrogenic cases	
	Pearson	Spearman	Pearson	Spearman	Pearson	Spearman
Age at diagnosis	.332	.311	.223	.229	.080	.085
Induction period	.183	.213	.287	.303	.027	.067

Table 5. Regressions of age at diagnosis on radium intake and exposure type.

Model	Constant	+ $\log_{10}$ Ra (μCi) x	+, if iatrogenic case	+, if iatrogenic case, $\log_{10}$ Ra (μCi) x
Constant difference	93.485	-16.034	11.181	-
Dose dependent difference	100.134	-18.246	-14.700	9.782
Exposure types combined	112.70	-21.677	-	-

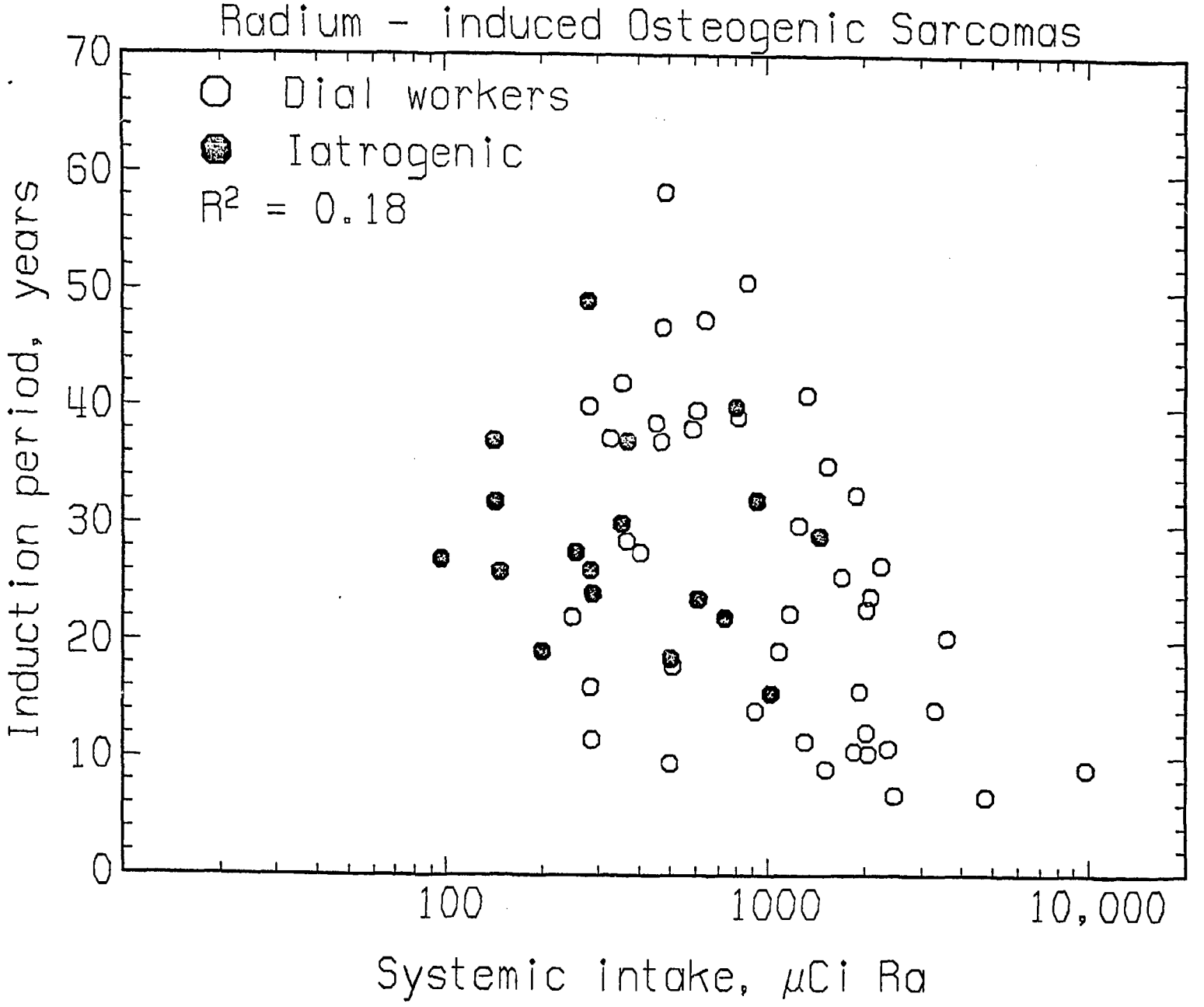
Radium - induced Osteogenic Sarcomas
Dial workers
Iatrogenic
R² = 0.18
Induction period, years
0
10
20
30
40
50
60
70
100
1000
10,000
Systemic intake, μCi Ra

Figure 1.

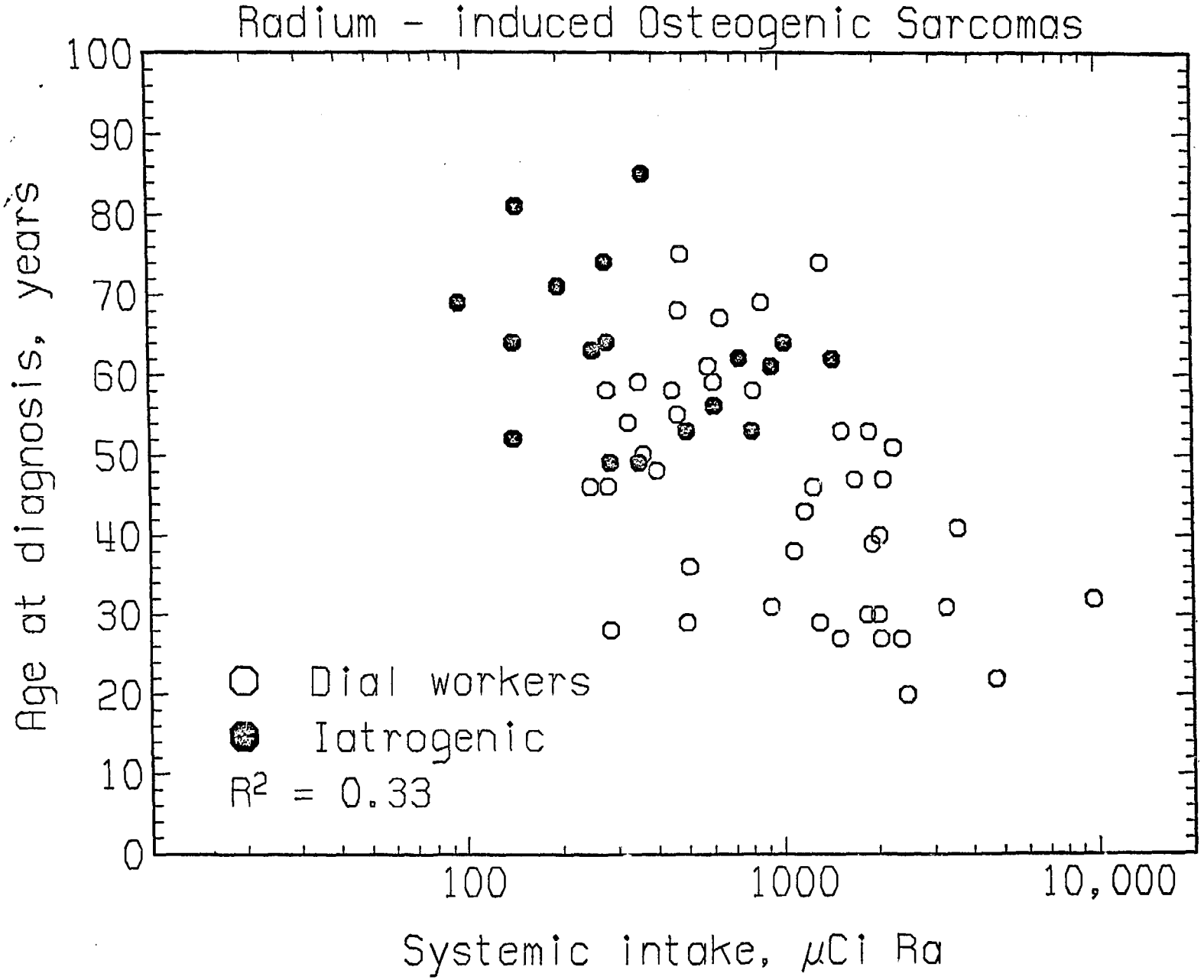
Radium - Induced Osteogenic Sarcomas
Age at diagnosis, years
Systemic intake, μCi Ra
Dial workers
Iatrogenic
R² = 0.33
0
10
20
30
40
50
60
70
80
90
100
100
1000
10,000

Figure 2.

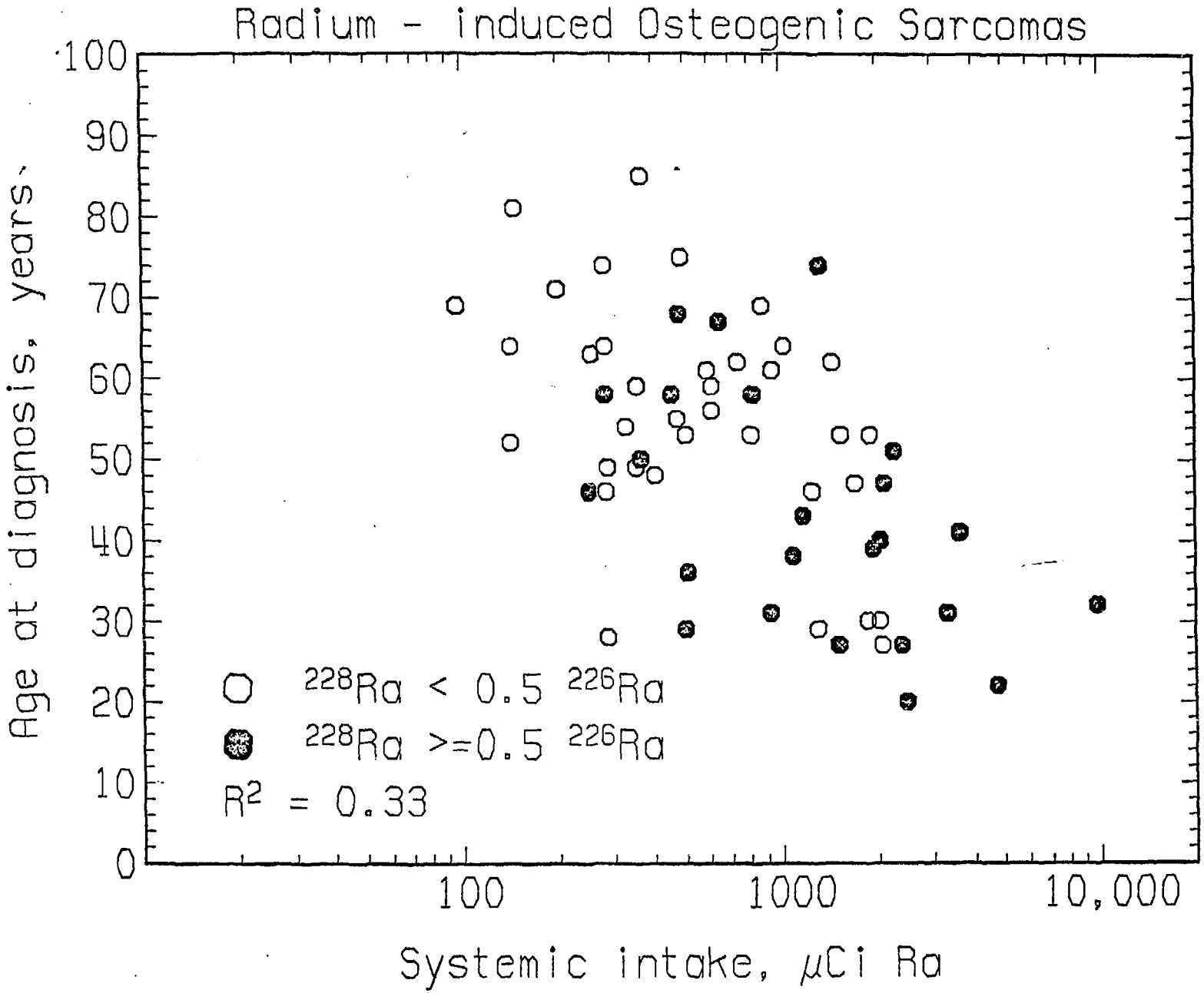
Radium - induced Osteogenic Sarcomas
Age at diagnosis, years
100
90
80
70
60
50
40
30
20
10
0
100
1000
10,000
Systemic intake, μCi Ra
228Ra < 0.5 226Ra
228Ra >=0.5 226Ra
R2 = 0.33

Figure 3.

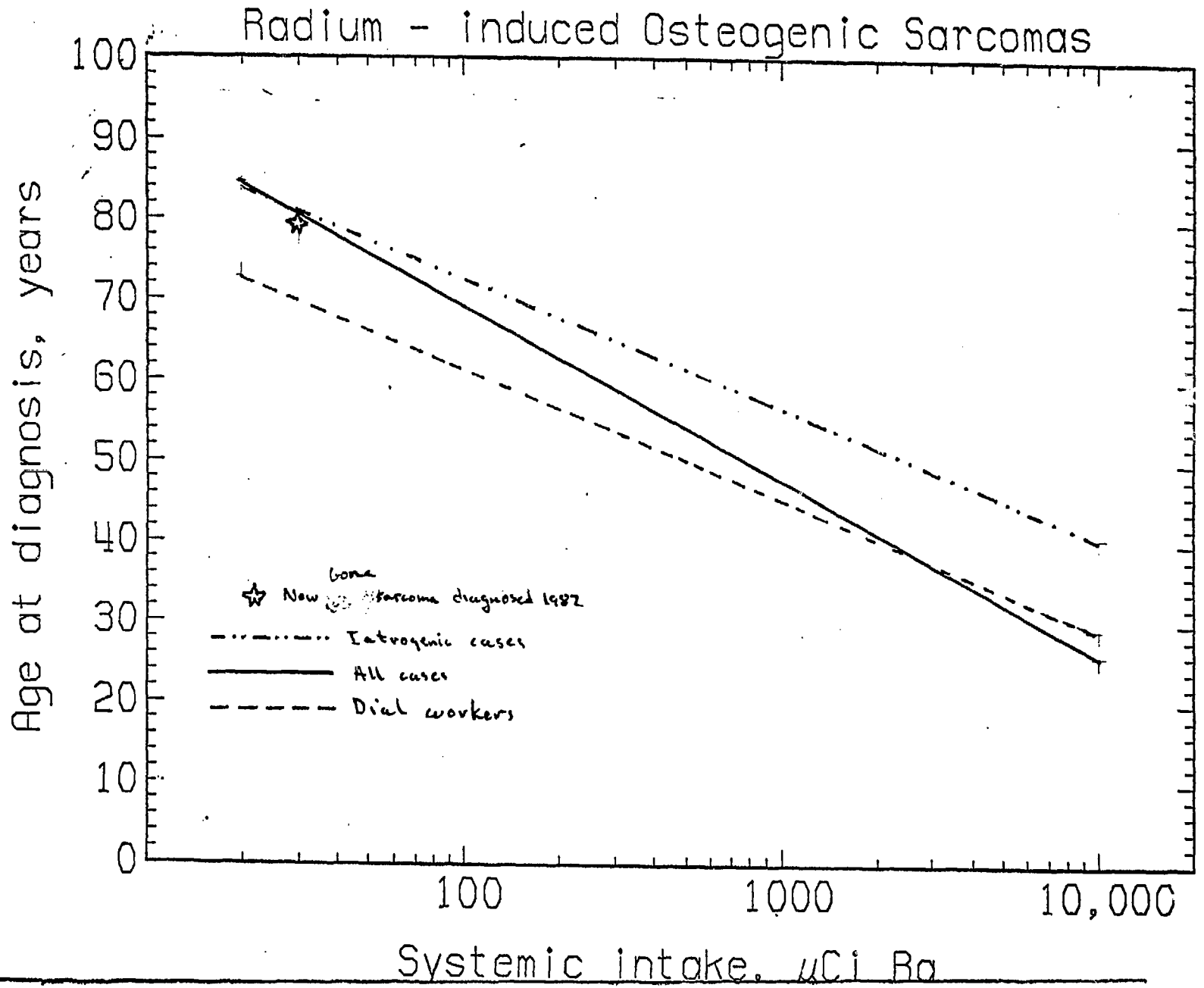
Radium - induced Osteogenic Sarcomas
Age at diagnosis, years
100
90
80
70
60
50
40
30
20
10
0
100
1000
10,000
Systemic intake, μCi Ra
Bone
New sarcoma diagnosed 1982
Iatrogenic cases
All cases
Dial workers

FIGURE 4.