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Cover Page Footnote
This work was initiated during a sabbatical leave from WIU for the period from August 20, 1990 to May 31, 1991 to visit the Argonne National Laboratory. The author wishes to thank and gratefully acknowledge the Biomedical Science Division of ANL for permission granted to work on the female radium dial painter data, T. J. Kotek for helping to familiarize me with database and Dr. Zhiyuan Liu for assisting me in calculating the AFE, DOE and TFE values listed in Tables 2-3.

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A Poisson Regression Model for Female Radium Dial Workers

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A Poisson regression model with interaction terms was applied to study the dose response relationship for radium-induced skeletal cancers. The model showed that the expected frequency count of bone tumors depended not only on the logarithmic dose and the time since first exposure, but also on the interaction between the logarithmic dose and the time since first exposure, whereas the dose-response model for head tumors depended only on the logarithmic dose.

Key words: Bone sarcoma, confounding factor, head carcinoma, interaction, Poisson regression model, radium dial painters.

Introduction

The tragedy of female dial painters attributed to radiation poisoning was one of the first widely known incidents of occupational hazards. Because it was a well-paying job many young women were attracted to work in the dial-painting industry in the United States. Unaware of radium poisoning, a common practice adopted by dial painters was to tip their brushes with their lips in order to provide a fine point for painting. The luminous paint usually contained 10 microcurie (μCi) per gram; as a result, dial painters were exposed to the intake of radium into their bodies. Several years after leaving the plant, the former dial painters began developing a variety of mysterious medical problems; the most common symptoms experienced were teeth and jaw problems. For the story of this deadly glow tragedy see Mullner (1999).

A new dose-response model is proposed, specifically a Poisson regression model, for radium-induced skeletal cancers, bone sarcoma (osteogenic sarcoma or fibrosarcoma) and head carcinoma (carcinoma of paranasal sinuses or mastoid air cells), which occurred among the U.S. female radium-dial painters. The dose-response relationship for radium-induced skeletal cancers is very important in the establishment of safety standards for the protection of the public health based on occupationally relevant exposure. Further, this study seeks to enhance understanding about the radiation effect of other α-emitting radio-nuclides (e.g., plutonium) for which there are no human data available. (To learn more about the effect of radium poisoning, see Evans (1966, 1967, 1980, 1981), Evans, et al. (1969) and Loutit (1970).)

Evans (1943) established the radiation protection standard of 0.1 μCi of radium in the adult human. In 1967, data from separate studies were consolidated into a newly created Center for Human Radiology (CHR) at Argonne National Laboratory (ANL). Based on a follow-up of this consolidated data by the end of 1976, Rowland, et al. (1978, 1983) established a quasi-log-linear model for the incidence rate of bone/head tumors as a function of the product between a quadratic function of exposure dose and an exponential function of exposure dose. They concluded that a model of dose-squared-exponential function provided the best fit for the bone sarcomas, and that an acceptable fit to the head carcinoma data was provided by the linear function of the dose. However, Rosenblatt, et al. (1971) showed that a plot of tumor incidence as a function of doses may potentially be erroneous and misleading. As a result, the theoretical support for Rowland, et al. chosen models might not be adequate.

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Based on this, a better dose-response model needs to be identified, and after reviewing literature on this topic, the author devised a different idea to model the dose-response curve. Because bone/head tumors are rare cancers, Poisson regression model was decided upon for use. The Poisson regression model has proven to be an effective statistical tool in the analysis of cancer death rates (Frome, 1983; Frome & Checkoway, 1985; Frome, et al., 1990). In 2006 Lee showed that the tumor frequency was supposed to be not only a function of exposure dose levels, but also potential confounding factors including the age at first exposure, the duration of exposure and the time since first exposure. However, the Poisson regression model proposed in that study did not consider the interaction between the exposure variable (dose) and potential confounding variables. This study incorporates all interaction terms into the Poisson regression model.

Methodology

Study Population

The study population was a cohort of 4,337 females employed in the U.S. radium-dial industry which was maintained by the CHR at ANL. This is exactly the same cohort as that used by Rowland, et al. (1978), except that the cohort was enlarged due to extra effort to collect additional subjects after 1976. After the data was first consolidated in the CHR at ANL in 1967, all located subjects were followed for vital status by the staff of the CHR. Death certificates were obtained as soon as staff at the CHR had knowledge of the death and was coded (8^{th} International Classification of Diseases) by the national Center for Health Statistics.

An attempt was made to contact all living subjects annually by mail, and subjects would be contacted by telephone if they did not respond to the mail inquiry. Details of follow-up method, follow-up period, dose measurement and others were given in Argonne's internal report (Radiological and Environmental Research Annual Report, 1984). Excluding those with unknown birth dates or without the social security numbers, 3,688 cases were usable (see Table 1). The measured population contained most of the known radium-induced skeletal cancers. About 973 living cases were still unmeasured despite efforts to obtain their cooperation. Most of these women refused because they did not wish to be reminded of their association with the radium industry or for other reasons not related to their current state of health. There were no known skeletal cancers in this group.

Exposure Data

Measurements of radium body burden were conducted by whole body counting and radon breath tests as subjects proceeded through a medical examination by a nurse and physician from the medical group of CHR at Argonne. At the time of radium body burden measurement all subjects also received a complete clinical examination, electrocardiography, blood chemistries and urine tests. Due to the interest in bone changes due to radium, extensive sets of x-rays emphasizing the skeleton were completed at each examination.

The complete measurement of radium in the body of a dial painter yielded two values, one for ^{226}Ra and one for ^{228}Ra. Because the ratio of ^{228}Ra to ^{226}Ra could vary with each batch of paint being used it was not possible to compare radium cases on the basis of the quantity of radium within the body. What was needed was a method of defining a radium equivalent, so that all measured cases could be expressed in the same units. Two ways to calculate the radium equivalent dose are available.

It was found that an effectiveness ratio (^{228}Ra to ^{226}Ra) was 1.5 when average skeletal doses were used and 2.5 when initial systemic intake was used a measure of the risk. Because the initial systemic intake was used in Rowland, et al. (1978), the initial systemic intake is also used herein to define the risk of the induction of bone sarcoma in a given dial painter: it is the intake of radium until the end of follow-up in 1984. The average values for each class interval were calculated as the arithmetic mean of their respective individual subject's data in that interval (see Tables 2-3).

Table 1: Female Radium Dial Workers with Known Status at the End of 1984

	Number	Average Age of 1st Exposure ± SD	Number Alive	Number Not Located	Cases Known to be Deceased	Malignancy	
						Bone Sarcoma	Head Carcinoma
Measured	1884	21.6 ± 6.2	1402	8	474	46	19
Unmeasured	1804	25.5 ± 9.3	973	175	656	18	5
Total	3688	23.5 ± 8.1	2375	183	1130	64	24

It is the sum of the activity of ^{226}Ra, in μCi, that entered the body plus two and a half times the activity of ^{228}Ra, in μCi, that entered the body. The head carcinoma was induced by radon (^{222}Rn) formed by decay of ^{228}Ra trapped within the air spaces in bone. Because the half-life of ^{222}Rn is only 55 seconds, it precludes its migration into these cavities; for this reason, ^{228}Ra was not considered and only ^{226}Ra activity was used for the systemic intake.

The panel data used for analysis of bone sarcomas and head carcinomas is summarized respectively in Tables 2 and 3. The interval sizes chosen were almost the same as that of Rowland, et al. (1978), except that the weighted average of systemic intake for the lowest dose < 0.5 and the highest dose > 1,000. The interval of the lowest dose < 0.5 is broken into two intervals, < 0.25 and 0.25-0.49; in contrast to Rowland, et al. who ignored the measured dose of subjects in the lowest level. Similarly, the range of the highest dose > 1,000 is broken into three intervals for bone sarcomas, designated as B1 (1,000-2,499, ≥ 2,500), and B2 (1,000-1,299, 1,300-1,599, 1,600-1,899, 1,900-2,199, 2,200-2,499, ≥ 2,500), and two intervals for head carcinomas, H1 (≥ 1,000) and H2 (1,000-1,499, ≥ 1,500). However, little difference in the estimated model parameters with respect to different interval sizes for doses greater than 1,000 μCi were concerned; thus, only B1 and H1 were used for the purpose of estimating regression coefficients.

Person-years were calculated from the year of first employment to the time of diagnosis of a bone sarcoma, of death, or to the end of 1984. Person-years were summed across cases within exposure levels to estimate the rate denominator. Although the estimated latent period of bone sarcomas followed a lognormal distribution with a median of 22.0 years (or 27.5 years) for all 64 cases (or 46 measured cases), it was decided not to subtract any fixed amount of time from the total person-years to obtain the person-years at risk. The inclusion of those first few years of experience could help establish more precisely the baseline risk (Thomas, 1987). The weighted average systemic intake for each class is the sum of person-year micro-curies for that class divided by the number of person years in the class. Similarly, the time required between first exposure to radium and diagnosis of head carcinoma follows a lognormal distribution with a median 37.5 years for all 24-head carcinomas; no assumed log time was subtracted from the calculated person-years to estimate person-years at risk.

Three possible potential confounding variables were considered: the age at first exposure (AFE) = age that a dial painter began to put the tip of the paint brush into her lips (years), the duration of exposure (DOE) = period of time that took between the start of putting the tip of the paint brush into her lips and stop such a practice (days), and the time since first exposure (TFE) = years since the first exposure

Table 2: Case Distribution and Bone Sarcoma Experience as a Function of Dose Level and Potential Time-Related Confounding Factors

B1: DOSE (Systemic intake/ $^{226}Ra + 2.5\times^{228}Ra$)		Number of Subjects	Person-Years (Years)	N (Bone Sarcoma)	Average Age at 1st Exposure (AFE, Years)	Average Duration of Exposure (DOE, Days)	Average Time Since 1st Exposure (TFE, Years)
Range (μCi)	Weighted Average (μCi)						
<0.25	0.04	881	35054	0	21.2	159.1	39.8
0.25-0.49	0.36	190	8176	0	21.7	233.5	43.0
0.5-0.99	0.72	172	7784	0	21.7	233.2	45.3
1.0-2.49	1.52	193	9782	0	19.7	212.6	50.7
2.5-4.9	3.59	96	5100	0	19.0	195.6	53.1
5-9.9	6.99	78	4281	0	19.5	119.5	54.9
10-24	16.46	73	4144	0	19.5	156.0	56.8
25-49	26.12	52	2932	1	19.4	156.2	56.4
50-99	69.73	21	1188	0	18.3	301.1	56.6
100-249	160.5	28	1472	1	18.3	307.8	52.6
250-499	374.3	36	1639	12	19.3	251.6	45.5
500-999	683.1	21	835	10	19.5	268.1	39.8
1,000-2,499	1665.4	26	611	18	18.8	157.9	23.5
≥2,500	3576.6	17	310	4	18.5	185.8	18.2

Table3: Case Distribution and Head Carcinoma Experience as a Function of Dose Level and Potential Time Related Confounding Factors

H1: DOSE (Systemic Intake/^{226}Ra)		Number of Subjects	Person-Years (Years)	N (Head Carcinoma)	Average Age at 1st Exposure (AFE, Years)	Average Duration of Exposure (DOE, Days)	Average Time Since 1st Exposure (TFE, Years)
Range (μCi)	Weighted Average (μCi)						
< 0.25	0.04	884	36155	0	32.2	158.9	40.9
0.25-0.49	0.35	213	9801	0	21.2	210.5	46.0
0.5-0.99	0.71	198	9487	0	21.3	210.9	47.9
1.0-2.49	1.53	237	12489	0	20.1	191.0	52.7
2.5-4.9	3.50	85	4630	0	19.1	217.8	54.5
5-9.9	6.90	50	2826	0	19.1	155.0	56.5
10-24.9	16.0	59	3402	0	19.3	197.6	57.7
25-49	35.3	40	2148	1	18.6	217.4	53.7
50-99	68.6	23	1141	1	18.2	370.6	49.6
100-249	175.	33	1303	6	17.9	143.4	39.5
250-499	364.	33	1379	6	19.2	259.2	41.8
500-999	616.	16	444	2	21.9	238.9	27.8
≥1,000	1566	13	289	3	17.8	179.2	22.2

Poisson Regression Model

Because bone sarcomas and head carcinomas are rare cancers, the frequency count (Y) of bone sarcomas (or head carcinomas) was assumed to follow a Poisson process, that is, the probability of N bone (or head) tumors is given by

$$P(Y = N) = e^{-\mu} \cdot \frac{\mu^N}{N!}, \text{ N} = 0, 1, 2, \ldots, (\mu > 0), \quad (1)$$

where μ denotes the expected count number of bone (or head) tumor. The tumor rate is Y/PYR, where PYR denotes the total exposure person years. Further, a Poisson regression model with interaction terms was applied to model the expected frequency counts of bone (or head) tumor as a function of logarithmic dose, temporal confounding factors together with their interaction with the logarithmic dose as follows:

$$\begin{aligned} \ln \mu = {} & \alpha_0 + \ln(PYR) + \alpha_1 LDOSE + \alpha_2 AFE \\ & + \alpha_3 DOE + \alpha_4 TFE + \alpha_5 LDOSE \cdot AFE \\ & + \alpha_6 LDOSE \cdot DOE + \alpha_7 LDOSE \cdot TFE \end{aligned} \quad (2)$$

where ln, the natural algorithmic function, of the left-hand side of (2) denotes link function, ln(PYR) is the offset (McCullagh & Nelder, 1989), and LDOSE is the natural logarithm of the weighted average systemic intake.

The reason the logarithm of the dose level (LDOSE) was used as opposed to the dose level was that the ratio between the highest to the lowest dose level was greater than 1,000. The method of maximum likelihood estimation was employed in computing the unknown regression coefficients (α_i's) of equation 2 by setting distribution = Poisson, link = log, and offset = ln(PYR) in the Proc GENMOD provided by the SAS package (SAS/STAT User's Guide, 1999). Based upon the well-formulated hierarchical principle, a backward elimination procedure was employed to retain the significant terms in equation 2 (Kleinbaum, et al., 1982). A criterion of the best fit is that the ratio of the scaled deviance divided by the degrees of freedom (d.f.) associated with the fitted model equals to one (Fleiss, et al., 2003).

Results

A total of 64 and 24 subjects were diagnosed with bone sarcomas and head carcinomas respectively. The prevalence for bone sarcoma (1.7% = 64/3,688) is 2.7 times as large as that (0.7% = 24/3,688) for head carcinoma (see Table 1). The reason for this significant difference in the incidence rate was that the head carcinoma seems to appear much later. The time of appearance for bone sarcoma was approximately 5 years, whereas 19 years for head carcinoma if the time of appearance was plotted against the initial systemic intake (Rowland, 1994). The highest systemic intake was the age at first exposure (AFE); values ranged from 16.0 to 21.7, which confirmed that the female radium dial workers were very young.

The average duration of exposure was shorter for low dose ranges than that for high dose ranges because the entire cohort in this study was comprised of two major sub-cohorts, pre-1930 and post-1930. A warning not put the tip of the paint brush into their mouth was issued by the government to workers in the dial painting industry in 1926; hence, workers in the post-1930 cohort received much less exposure. Similarly, the average time since first exposure (TFE) value for the class over 2,500 μCi was only 18.2 years which was far shorter than those in the range of less than 1,000 μCi. This was because most of 17 measured in that class were already diseased. Incidentally, the highest systemic intake was 6,331 μCi.

Table 4 shows the parameter estimate, standard error/p-value and scaled deviance/degrees of freedom associated with each of the risk factors used in (2) for the dataset B1. Using the p-value < 0.05 as a criterion for variable inclusion, the final models for the bone tumor that represent the dataset B1 is given respectively by

$$\begin{aligned} \ln \mu = {} & 4.8 - 1.2 \cdot LDOSE - 0.4 \cdot TFE \\ & + 0.051 \cdot LDOSE \cdot TFE \end{aligned}, \quad (3)$$

Table 4: Estimated Regression Coefficients (p-value) and Scaled Deviance (degrees of freedom) for Bone Sarcoma

Data Set	Intercept (p-value)	LDOSE (p-value)	TFE (p-value)	LDOSE*TFE (p-value)	Scaled Deviance (d.f.)
B1	4.78 (0.38)	-1.19 (0.09)	-0.36 (0.002)	0.051 (0.001)	6.12 (10)

for dataset B1, the interaction term LDOSE×TFE was significant. As a result, LDOSE and TFE (the lower order term) were retained in the model, even though the p-value for the term of LDOSE (p-value = 0.09) in equation was not significant.

Table 5 shows the parameter estimates, standard errors, p-value, model deviances and degrees of freedom after fitting Poisson model of (2) to dataset H1. According to Table 5, the Poisson models for H1 is given respectively by

$$\ln \mu = -11.29 + 0.978 \cdot LDOSE \,. \qquad (4)$$

Discussion

Time since first exposure (TFE) (see eq. 3), shown as a confounding factor, had an effect on the occurrence of bone sarcomas in addition to the logarithmic dose. Worse, a significant interaction existed between the logarithmic dose and the time since first exposure: This implies that, for different time since first exposure, the effect of the logarithmic dose on the expected frequency of bone tumors is different. In other words, time since first exposure is an effect modifier (Kleinbaum, et al., 1982). By contrast, time since first exposure is neither a confounder nor an effect modifier for the expected frequency of head carcinomas. An advantage of using the logarithmic dose level is reflected in that it is not necessary to be concerned if the term of dose-squared or the term of power higher than two is included or not. From a Taylor's series expansion, ln(DOSE) contains all powers of DOSE in the model.

The Environmental Protection Agency proposed the maximum level for radium in drinking water to be set at 5 pCi/liter, where pCi denotes picocurie and one picocurie, one-trillionth of a curie (Train, 1975). Using the generally accepted values of 2.2 liters of water consumed per day and a gut absorption rate of 21%, the systemic intake calculated by Rowland, et al. (1978) is 843 pCi of ^{226}Ra. Using the linear model for head carcinoma, the incidence rate after 1-year intake calculated by Rowland, et al. is 1.3×10^{-8}. However, by using equation 4, the incidence rate for head carcinomas is 1.2×10^{-5}. In a comparison with this estimate, the Rowland, et al. (1978) estimate seems too conservative. Rowland, et al. did not calculate the rate for bone sarcoma, however, using equation 3, the rates for bone sarcomas were 3.4, 0.09, 0.002, and 6.2×10^{-5}, respectively for TFE = 10, 20, 30, and 40 years.

Although the data for the frequency of bone/head tumors seemingly have excessive zeros over a wide range of logarithmic dose levels, the zero-inflated Poisson model (Lambert, 1992) was not able to be used for datasets B1 or H1 because it was not possible to model its frequency as a mixture of two models: one is a degenerated point mass function at zero count and the other is a Poisson model for count greater than one. When attempted using the SAS Proc GENMOD, the scaled deviance (36.7) was much larger than its degrees of freedom (11).

Baum (1973) claimed that the dose-response curve of radiation induced tumors was often represented by a power function of dose with exponents less than one. By using the atomic bomb of surviving population in

Table 5: Estimated Regression Coefficients (p-value) and Scaled Deviances (degrees of freedom) for Head Carcinoma

Data Set	Intercept (p-value)	LDOSE (p-value)	Scaled Deviance (d.f.)
H1	-11.29 (< 0.0001)	0.978 (< 0.0001)	7.51 (11)

Hiroshima and Nagasaki, Japan, Baum found that for data on leukemia in Hiroshima and Nagasaki, the dose-response curve was adequately represented by power functions of dose with exponents between 0.65 and 1.0. However, in view of results from this study, the expected frequency was a function of not only the logarithmic dose, but also potential time-related confounding factors (time since first exposure) and the interaction between the logarithmic dose and time since first exposure. Hence, Baum's claim for the dose-response relationship is clearly invalid.

Recent studies have also addressed other aspects of radiation poisoning among U.S. radium dial workers. Carnes, et al. (1997) adopted Cox's (1972) hazard regression to build a dose response model. Although they incorporated AFE, a time-related confounding factor, into their model, the AFE was shown to be insignificant according the Poisson model used in this study. In addition, Carnes, et al. did not consider interaction in their study. An overview of studies of the U.S. radium dial workers was presented by Fry (1998). In addition, Rentztzi (2004) addressed the case of radium dial workers as human experimentation with radiation harmful effect.

Conclusion

Using the Poison regression model, data regarding radiation poisoning among female radium dial workers were re-analyzed. A dose-response model was obtained respectively for bone sarcoma and head carcinoma. The model showed that the expected frequency of bone sarcomas was not only a function of the logarithmic dose and the time since first exposure, but also the interaction between the logarithmic dose and the time since first exposure, whereas the dose-response model for head carcinomas was a function of the logarithmic dose only. Among all dose-response models available in the literature, the Poisson regression model proposed in this article was deemed best because it is simple, precise and informative.

Acknowledgements

This work was initiated during a sabbatical leave from WIU for the period from August 20, 1990 to May 31, 1991 to visit the Argonne National Laboratory. The author wishes to thank and gratefully acknowledge the Biomedical Science Division of ANL for permission granted to work on the female radium dial painter data, T. J. Kotek for helping to familiarize me with database and Dr. Zhiyuan Liu for assisting me in calculating the AFE, DOE and TFE values listed in Tables 2-3.

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