MASTER

AN EVALUATION OF SEVERAL METHODS FOR ASSESSING
THE EFFECTS OF OCCUPATIONAL EXPOSURE TO RADIATION

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ABSTRACT

The evaluation of health effects in populations occupationally exposed to low-level ionizing radiation is a matter of considerable current controversy. The analysis of data on such exposures presents a variety of problems resulting from the time dependent nature of the exposure data, certain selective biases found in working populations, and particularly limits imposed by the size of the populations, and the magnitudes of exposures received. In this paper, several methods of analysis are presented and evaluated using data from the Hanford plant for illustration. Questions of interest include whether or not to utilize an external control, and how to handle the highly skewed exposure data most effectively. Expressions for the power of various procedures are used not only to compare methods but also to evaluate the potential for detecting effects in occupationally exposed populations.

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INTRODUCTION

Assessing the health effects of chronic low-level exposures to radiation poses a number of challenging problems in analysis. Many of these problems are well illustrated by a current study of the effects on mortality of occupational exposure to ionizing radiation at the Hanford plant.

The Hanford plant, which is located in southeastern Washington, was established in the early forties as an installation for plutonium production. Many of the workers employed by the various contractors hold jobs involving some exposure to radiation. Yearly records of this exposure, obtained from dosimeter readings, as well as occupational data, are maintained for all employees. Mortality data are obtained by having the Social Security Administration periodically search their records for deaths of persons identified in the personnel rosters of Hanford contractors.

In my presentation today I plan to discuss some of the problems involved in analyzing such data and to illustrate certain methods of analysis with data from the Hanford plant. I will also compare certain approaches by presenting the results of power calculations.

RADIATION EXPOSURE DATA

Figure 1 shows the distribution of dose accumulated through 1976 for 15,134 monitored white males employed at Hanford at least two years. This

group, which constitutes the study population for all analyses in this paper, is the group which has received nearly all of the radiation exposure at Hanford. The highly skewed distribution reflects the fact that most Hanford workers are not regularly involved in radiation work so that a relatively small number of workers (less than 15% of the work force) receive annual whole body doses in excess of 1 rem with a very small number of these exceeding 4 rem per year (less than 1% of the work force).

The nature of this distribution has a definite impact on the choice of analysis. First, because of the considerable variability in the radiation exposures received, methods of analysis which relate death rates directly to exposure are probably less subject to bias and more powerful against alternatives of positive radiation effects than methods based on comparison of the entire study population with an external control. Second, the highly skewed exposure distribution means that caution must be exercised in applying and interpreting methods which are based on the assumption of approximate normality. Grouping of exposures, which of course involves some loss of information, is appealing both from the standpoint of alleviating the skewness problem and because the presentation of results may be clearer. Both the question of internal vs. external comparisons and the question of grouping vs. not grouping will be considered in more detail later in this presentation.

Figure 1 indicates that a total of 67,850 rem have been received at Hanford. If we use the BEIR I [1] estimate that 1 rem increases the risk of cancer death by 5 cases per 10^{-6} rem per year, we would expect only 4 or 5 radiation induced cancer deaths in this population even if there were no latent period. Since several hundred "spontaneous" cancer deaths would be expected in this population (based on U.S. mortality rates), it is unlikely that such a

small increase will be statistically detectable. In spite of these limitations, it is important to study occupationally exposed populations such as Hanford primarily to evaluate the hypothesis that effects might be many times larger than our current estimates would suggest. One goal of this paper is to quantitate these limitations better by presenting the results of power calculations.

Radiation exposure at Hanford is correlated with a number of variables that may also affect mortality. Because exposure is gradually accumulated over time and because few doses over one rem were received during the early period of plant operation, cumulative exposure is highly correlated with calendar year. Because we have no record of exposure after workers leave Hanford, recorded cumulative exposure is highest for those workers who remain employed in the industry and who are probably most subject to the various selective biases often referred to as the "healthy worker effect." Finally, most of the higher exposures have been received by workers in a few specific occupations, all classified as craftsmen or operators. Thus there are a number of potentially biasing factors that must be considered in analysis of this data. More detailed discussion of these factors and their impact on analysis is provided in earlier papers [2,3].

METHODS OF ANALYSIS

The basic principle of the analyses that we have conducted is to compare the doses of those workers dying from a particular cause to the doses of comparable workers at risk of dying at the same time. For example, suppose that worker i dies in 1967 at age 56 with cumulative dose z_{i67} . We might then compare z_{i67} with the cumulative doses (up to 1967) for workers who are alive and at risk of dying at the beginning of 1967 and who are age 55-59 at the time.

We will call the set of doses of those workers alive in 1967 and of similar age the risk set for worker i and denote this set by R_i . Variables other than age can of course be considered in defining this risk set. We will denote the mean of the doses in R_i by μ_i and the variance by σ_i^2 .

Most of the workers whose doses are included in R_i will survive 1967 and many will accumulate additional exposure after 1967. However, for the purposes of this comparison with worker i , it is appropriate to consider only exposure that has been accumulated up to 1967. Otherwise, the analysis will be biased toward a positive correlation of survival and exposure simply because those workers that survive the longest have the most opportunity to accumulate exposure.

Functions of exposure other than the cumulative exposure at the time of risk can be considered. With a view to taking into account a latent period, exposures might be lagged for various intervals. For example, we might consider only exposures accumulated five years prior to death or as of 1962 in the above example. Another alternative might be to group exposures into two or more categories. In this case z_{it} would denote a score indicating the exposure category of worker i at time t .

The approach that is used to obtain a statistical test is to compare the observed score

$$Z = \sum_{i=1}^n z_{it_i}$$

with the expected score $\mu = \sum_{i=1}^n \mu_i$ where i indexes deaths from a particular cause and z_{it_i} is some measure of dose for worker i at the time of death t_i . The test can be regarded as a permutation test of Z , conditional on the risk

sets R_i , Asymptotically, the statistic

$$Y = \frac{Z - \mu}{\left[\sum_{i=1}^n \sigma_i^2 \right]^{1/2}}$$

will have a standard normal distribution.

The above approach can be regarded as a simple application of Cox's [4] proportional hazard model in which the time variable is calendar year grouped in single year intervals, in which there is a single time dependent regression variable, dose, and in which other variables such as age are controlled through stratification. A more detailed description of the above methodology, including the adaption of Cox's model for use with the Hanford data, is given in [2].

Evaluating the null distribution of Y is difficult in view of the extremely skewed data. We have considered two possible solutions. In the analysis of cumulative doses we have adjusted a normal approximation by using the third and fourth null moments of Z . This method makes use of an Edgeworth series and is described in Cramer [5]. A second solution is to group exposures and to use an exact permutation test in cases of particular interest.

For the analyses presented in this paper, deaths occurring over the period January 1, 1947 through April 30, 1977 are grouped into one-year intervals. Stratification variables are age (in five-year intervals), occupation (craftsmen-operators and other workers), and employment status (employed and terminated). Some of these variables are time dependent so that workers will move from one stratum to another as they are followed forward in time. Exposures are lagged for two years.

The method is illustrated for myeloid leukemia in Table 1. There were 8 deaths from this cause in the study population with total exposure Z (two years

prior to death) of 16.03 rem. The total of the means from the five risk sets was 21.05 rem with a total variance of 178.58 rem². We then have $Y = -0.38$ so that this population exhibits no evidence of radiation induced leukemia at this time.

The analysis described above has been applied to all causes of death, all malignant neoplasms, and several specific cancer types with the results summarized in Table 2. For most causes of death there is no evidence of a positive association with radiation exposure, a result which is quite consistent with our current estimates of radiation effects.

There are two specific cancer types which exhibit significant positive correlations with radiation exposure - multiple myeloma and cancer of the pancreas. Both inferences are based on a small number of deaths with high exposures. For example, the inference for multiple myeloma results from three deaths with high exposures of 20.0, 27.0 and 34.4 rem compared with the respective expected values of 3.8, 7.1 and 3.8 rem. For cancer of the pancreas, the difference between observed and expected totals results almost entirely from four deaths with exposures of 16.9, 26.9, 28.3 and 45.9 rem compared with the respective expected doses of 6.2, 5.8, 7.7 and 13.7 rem. The possibility that these are false positive findings or that other factors, such as occupational exposure to other agents at Hanford or elsewhere, are the underlying causes of one or both of the correlations cannot be ruled out. Furthermore, death certificate diagnosis of cancer of the pancreas is not very reliable. There is evidence from other studies [1], that multiple myeloma and cancer of the pancreas have been induced by radiation, but it is not nearly as substantial as that for a number of other cancer types, the most notable being myeloid leukemia. A more complete discussion of the interpretation of these results is provided in [3].

We have conducted a variety of alternative analyses to that presented in Table 2. We have lagged exposures by 0, 2 and 10 years, and have considered a variety of combinations of stratification variables. Although the p values fluctuate with different approaches, in no case have we obtained evidence of a positive correlation of radiation exposure and death from all cancers or from any specific cancer type other than multiple myeloma and cancer of the pancreas. When exposures are lagged for 10 years, cancer of the pancreas fails to exhibit a significant correlation.

An alternative analysis, to which I would like to give more than passing attention, is one in which exposures are grouped. That is, instead of analyzing the original doses, exposures are grouped into four categories: 0-2 rem, 2-5 rem, 5-15 rem, and 15+ rem. The observed deaths in each category are then compared with those expected if radiation exposure had no effect. This type of analysis is commonly known as a Mantel-Haenszel [6,7] approach, but can also be derived using the approach described above by replacing the actual doses with scores for the exposure categories. We have used the average dose in each category as the score for that category. A more detailed description of this method of analysis as applied to the Hanford data is given in [3].

The results of this analysis are given in Table 3. The calculation of expected deaths is based on the assumption of no radiation effect and does not involve the use of rates from an external population. A positive correlation of mortality and radiation exposure is indicated by a generally increasing ratio of observed to expected deaths with increasing exposure. Results are quite similar to those presented in Table 2 except that the correlation for cancer of the pancreas is no longer statistically significant. In Table 3 we see clearly that the observed correlations result from a very small number

of deaths in the highest exposure category (15+ rem). Grouping exposures does result in some loss of information and of course results may depend on the particular choice of cutpoints. However, the skewness problem is somewhat alleviated (for multiple myeloma it was feasible to carry out an exact permutation test on the grouped data), and the format of the results as presented in Table 3 makes it somewhat clearer that the correlations observed do result from a very small number of deaths. I might note here that the fact that this is a rather controversial subject means that many people without statistical training are interested in the findings. For this reason, I feel that the methods used not only need to be sound according to statistical and epidemiological principles, but also must be understandable to those not trained in these disciplines.

POWER CALCULATIONS

Earlier in this paper it was stated that the real rationale for studying a population such as Hanford was to investigate the hypothesis that effects might be many times larger than our current estimates would suggest. One goal of this section is to quantitate the potential of the Hanford data by presenting the results of power calculations. A second goal is to compare the power of different methods of analysis. The theoretical basis for developing the formulae necessary for the power calculations is given in the appendix.

In order to calculate power, a model for the form of the alternative hypothesis must be specified. The model used for the calculations to be presented today is the relative linear model where the risk of dying of a particular cancer at time t for a person in stratum x and with exposure z is given by

$$\lambda(t,z,x) = \lambda(t,x)[1 + \beta z] \quad (1)$$

where $\lambda(t,x)$ denotes the "spontaneous" risk of a person in stratum x dying of the particular cancer at time t . The linear model is chosen because it is relatively easy to work with and because it is the basis for our current estimates of radiation effects.

Such estimates are derived by linear extrapolations from effects at high levels of exposure such as those experienced by Japanese survivors at Hiroshima and Nagasaki and by British patients treated with irradiation for a disease called ankylosing spondylitis. Dose-response curves obtained from animal experiments suggest that linear extrapolation is likely to be conservative in that it overestimates effects at low levels. These estimates are expressed both in terms of a relative or multiplicative linear model in which the risk from radiation is assumed to be proportional to the risk from other carcinogens ("spontaneous" risk), and the additive linear model in which the risk from exposure is assumed to be constant for all segments of the population. Although the additive model is useful from the standpoint of radiation protection, the relative model is supported by several studies of radiation effects [8].

In order to calculate the power for any procedure, even for an analysis which does not utilize an external control, it is necessary to specify the $\lambda(t,x)$. That is, we must consider the occurrence of death as a random variable. The $\lambda(t,x)$ are taken to be age-specific death rates for the U.S. white male population for the period 1968-1973. Power calculations are made for the time period 1960-1977 (very little exposure had been accumulated prior to 1960), and it is assumed that the analyses are controlled for age and calendar year. It is also assumed that hypotheses are tested at the 0.05 level using a one-tailed test.

Results of power calculations are presented for leukemia (Table 4 and Figures 2 and 4) and for all cancers combined (Table 5 and Figures 3 and 5).

For leukemia, calculations are presented over the range $\beta = 0$ to 30% per rem per year while for all cancers the range is $\beta = 0$ to 3% per rem per year. (Recall that β is the proportional increase over spontaneous rates λ as indicated in Equation 1.) Our current estimates of these effects (β) as presented in the BEIR report [1, p. 171] are 2% per rem per year for leukemia and 0.2% per rem per year for all cancers combined. Thus the range of β evaluated is 0 to 15 times current estimates of effects. It is assumed that each β evaluated applies for the time period two or more years beyond the occurrence of the exposure. This assumption is not unreasonable for leukemia, but is not realistic for other cancers which probably have latent periods of at least 10 years. Roughly, the calculations for all cancers combined can be considered as applying to some time period in the future.

In Figures 2 and 3 and Tables 4 and 5, power curves are presented for a procedure in which the number of deaths observed is compared to the number expected based on U.S. rates for the white male population. The procedure is evaluated for the case where the total study population is considered as well as as for the case where the calculations are restricted to that segment of the population that has accumulated X or more rem exposure (with $X = 5$ and 15). Restricting the calculation to those with higher exposures clearly results in greater power for detecting both leukemia and cancer effects.

In Figures 4 and 5 and Tables 4 and 5, results are presented for the completely internal comparisons described earlier in this paper. Calculations have been made for the analysis of individual doses and for a grouped analysis with two exposure groups (0-15 rem and 15+ rem). Power calculations for analysis of four exposure groups have not yet been completed. As expected, the analysis utilizing individual doses has the greater power. Presumably

an analysis utilizing four exposure groups would have power in between the power of the procedures compared in Figures 4 and 5.

For detecting leukemia effects, the internal comparison of individual doses and the comparison of those with 15+ rem and 5+ rem with the U.S. population all have similar power. For detecting cancer effects, the power of the comparison utilizing those with 5+ rem falls below the other two procedures. The comparison of the entire study population with the U.S. population has substantially lower power than the other procedures, particularly for detecting cancer effects. In interpreting these results, it should be noted that results of calculations utilizing a single cutpoint could be quite dependent on the shape of the true dose-response curve. It should also be noted that the power of the procedures which utilize U.S. rates will be reduced in the presence of a "healthy worker effect." (Previous analyses indicate that Hanford workers have lower death rates for most causes than those of the general U.S. population.) These considerations might well lead us to favor an internal comparison utilizing either individual doses or several exposure categories.

The results presented above provide some indication of the potential of occupational exposure studies for detecting radiation effects. If the internal comparison utilizing individual doses is used we have an 18% chance of detecting a leukemia effect equal to our current estimates, a 70% chance of detecting an effect 5 times current estimates, and a 94% chance of detecting an effect 10 times current estimates. The power for detecting cancer effects is considerably lower and cannot be expected to apply until sometime in the future in view of a probable latent period.

The power calculations above must be interpreted with caution since the calculations require many assumptions and approximations. Asymptotic normality

has been utilized with very skewed distributions and small samples sizes. No account has been taken of the measurement error involved in dosimeter readings of radiation exposure. The true power of various procedures is likely to be somewhat lower than that presented in Tables 4 and 5.

REFERENCES

1. Advisory Committee on the Biological Effects of Ionizing Radiations, National Academy of Sciences-National Research Council, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. U.S. Govt. Printing Office, Washington, DC, 1972.
2. E. S. Gilbert, The assessment of risks from occupational exposures to ionizing radiation. Energy and Health, Society for Industrial and Applied Mathematics, Philadelphia, 209-225, 1979.
3. E. S. Gilbert and S. Marks, An analysis of the mortality of workers in a nuclear facility. Radiat. Res. 79, 122-148 (1979).
4. D. R. Cox, Regression models and life-tables, J. Stat. Soc. B 34, 187-220 (1972).
5. H. Cramer, Mathematical Methods of Statistics, Princeton University Press, 227-231, 1945.
6. N. Mantel and W. Haenszel, Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22, 719-748 (1958).
7. N. Mantel, Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother. Rep. 50, 163-170 (1966).
8. P. G. Smith, Some problems in assessing the carcinogenic risks to man of exposure to ionizing radiation. Energy and Health, Society for Industrial and Applied Mathematics, Philadelphia, 61-80, 1979.
9. International Classification of Diseases, Adapted for Use in the United States, 8th rev., PHS Publication No. 1693, U.S. Govt. Printing Office, Washington, DC 1967.

TABLE 1. Analysis of deaths from myeloid leukemia.
Exposures lagged for two years. (See
text for complete details.)

<u>Year of Death</u>	<u>Age at death</u>	<u>Observed Dose Z_i</u>	<u>Expected Dose μ_i</u>	<u>σ_i^2</u>	<u>Number in risk set R_i</u>
70	56	0	0.66	1.18	359
76	70	0.18	1.51	2.80	241
68	59	0.30	1.24	5.88	191
72	64	0.40	3.89	37.12	307
69	39	1.04	3.45	21.39	578
76	67	1.29	3.98	38.19	68
76	61	1.38	1.93	19.32	462
69	67	<u>11.44</u>	<u>4.40</u>	<u>52.70</u>	166
	TOTAL	16.03	21.06	178.58	

$$\gamma = \frac{16.03 - 21.06}{[178.58]^{1/2}} = -0.38$$

TABLE 2. Results of analysis of exposures lagged for two years.^a

Cause of Death	Number of Deaths (n)	Observed Mean (Z/n)	Expected Mean (μ/n)	Normal Deviate (y)	Adjusted p-value (one-tailed)
All Causes	2410	2.27	2.36	-0.98	0.84
All Malignant Neoplasms (M.N.) (140-209) ^b	487	2.46	2.57	-0.46	0.67
M.N. of Buccal Cavity (140-149)	19	1.70	2.62	-0.74	0.74
M.N. of Stomach (151)	31	3.21	2.26	1.00	0.15
M.N. of Colon (153)	46	1.63	2.02	-0.62	0.71
M.N. of Pancreas (157)	33	4.90	3.15	1.79	0.048
M.N. of Other Digestive Organs (150,152, 155-156)	38	0.66	1.57	-1.54	0.96
M.N. of Lung (162)	143	3.15	3.10	0.10	0.44
M.N. of Prostate (185)	34	1.69	3.00	-1.30	0.92
M.N. of Brain (191-192)	17	2.38	2.25	0.12	0.40
Lymphosarcoma and Reticulum Cell Sarcoma (200)	17	1.09	2.04	-0.89	0.80
Hodgkin's Disease (201)	7	1.57	1.57	-0.00	0.42
Myeloid Leukemia (205)	8	2.00	2.63	-0.38	0.56
Other Leukemia (204, 206-207)	4	0.19	1.93	-0.77	0.71
Multiple Myeloma (203)	8	10.40	2.59	4.40	0.0004
Other Neoplasms of Lymphatic and Hematopoietic	4	0.25	1.76	-0.66	0.60
All Other Cancers	78	1.61	2.42	-1.40	0.92
All Non-Cancer Causes	1884	2.21	2.30	-0.86	0.80
No Certificate	39	2.62	2.73	-0.17	0.51

^aSee text for complete details.

^bCoded according to the Eighth Revision of the International Classification of Diseases. [9].

TABLE 3. Observed and expected deaths due to selected causes by exposure category for monitored white males employed at least two years. Exposures are lagged for two years.^a

Person Years Cause of Death	Exposure Category								Exposure Score for Trend Test		Probability of Trend Arising Due to Chance ^c
	0-2 rem		2-5 rem		5-15 rem		15+ rem				
	Obs.	Exp. ^b	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	
All Causes	1905	1831.2	267	269.5	146	150.3	92	99.0	2.2	2.3	0.83
All Malignant Neoplasms (140-209) ^d	372	376.5	66	56.3	29	31.6	20	22.6	2.4	2.5	0.72
M.N. of Buccal Cavity (140-149)	17	14.6	0	2.3	2	1.2	0	0.9	1.4	2.5	0.86
M.N. of Stomach (151)	24	25.2	4	2.9	0	1.6	3	1.2	3.3	2.2	0.09
M.N. of Large Intestine (153)	37	37.2	7	4.9	1	2.5	1	1.5	1.6	2.0	0.75
M.N. of Pancreas (157)	23	23.4	5	4.7	1	3.0	4	1.9	4.2	3.0	0.11
M.N. of Other Digestive Organs (150, 152, 155-156)	35	32.7	3	2.9	0	1.5	0	0.9	0.7	1.6	0.94
M.N. of Lung (162)	95	105.4	25	18.4	16	10.8	7	8.4	3.1	2.9	0.34
M.N. of Prostate (185)	26	25.3	6	4.2	2	2.4	0	2.0	1.4	2.9	0.94
M.N. of Brain (191-192)	11	13.2	4	2.1	2	1.1	0	0.6	2.1	2.3	0.58
Lymphosarcoma and Reticulum Cell Sarcoma (200)	14	13.9	2	1.6	1	0.9	0	0.6	1.3	2.1	0.78
Hodgkins Disease (201)	5	5.7	2	0.8	0	0.5	0	0.1	1.3	1.6	0.62
Myeloid Leukemia (205)	7	5.6	0	1.5	1	0.7	0	0.3	1.5	2.5	0.73
Other Leukemia (204, 206-207)	4	3.4	0	0.3	0	0.2	0	0.2	0.5	2.1	0.74
Multiple Myeloma (203)	5	6.2	0	0.7	0	0.6	3	0.5	9.9	2.8	0.006 ^e
Other M.N. of Lymphatic and Hematopoietic Tissue (202, 208-209)	4	3.3	0	0.4	0	0.2	0	0.1	0.5	1.8	0.73
All Other M.N.	65	61.5	8	8.7	3	4.3	2	3.5	1.7	2.4	0.88
All Non-Cancer Causes	1501	1485.7	200	207.8	114	115.9	69	74.6	2.2	2.3	0.81
No Certificate	32	29.0	1	5.3	3	2.9	3	1.8	3.1	2.6	0.27

^aSee text for complete details.

^bExpected deaths are calculated from the experience of all workers in the exposure study, allowing for age, calendar year, occupation, and employment status.

^cThe significance levels are for a one-tailed test and are calculated using a normal approximation.

^dCoded according to the Eighth Revision of the International Classification of Diseases [9].

^eThis probability calculated exactly.

TABLE 4. Power of detecting leukemia effects
for five methods of analysis.

	<u>Comparison with U.S. Rates</u>			<u>Internal Comparisons</u>	
	<u>Total Study Population</u>	<u>5+ rem Only</u>	<u>15+ rem only</u>	<u>Individual Doses</u>	<u>15+ rem vs. <15 rem</u>
$\beta = 0$	0.05	0.05	0.05	0.05	0.05
0.02	0.10	0.16	0.19	0.18	0.16
0.05	0.19	0.38	0.44	0.41	0.35
0.10	0.43	0.71	0.73	0.70	0.62
0.15	0.67	0.88	0.88	0.87	0.80
0.20	0.84	0.96	0.95	0.94	0.90
0.25	0.93	0.98	0.98	0.98	0.95
0.30	0.97	1.00	0.99	0.99	0.98

TABLE 5. Power of detecting cancer effects
for five methods of analysis.

	<u>Comparison with U.S. Rates</u>			<u>Internal Comparisons</u>	
	<u>Total Study Population</u>	<u>5+ rem only</u>	<u>15+ rem only</u>	<u>Individual Doses</u>	<u>15+ rem vs. <15 rem</u>
$\beta = 0$	0.05	0.05	0.05	0.05	0.05
0.002	0.07	0.09	0.10	0.10	0.09
0.005	0.11	0.17	0.20	0.21	0.17
0.010	0.20	0.38	0.45	0.47	0.37
0.015	0.32	0.61	0.70	0.72	0.60
0.020	0.47	0.81	0.86	0.88	0.78
0.025	0.62	0.92	0.95	0.96	0.90
0.030	0.75	0.97	0.98	0.99	0.96

FIGURE 1. Distribution of cumulative doses for white males employed at least 2 years.

FIGURE 2. Power curves for leukemia using a comparison with U.S. rates.

FIGURE 3. Power curves for cancer using a comparison with U.S. rates.

FIGURE 4. Power curves for leukemia using internal comparisons.

FIGURE 5. Power curves for cancer using internal comparisons.

APPENDIX

In this appendix expressions are derived for evaluating the power of several procedures for testing the null hypothesis of no radiation effect. Notation similar to that used in describing the proportional hazards model of Cox [4] is used. That is, let t denote calendar time (in single year intervals), x denote a particular stratum (based on age and other variables). Let $R(t,x)$ denote the set of workers in stratum x alive at time t and $N(t,x)$ denote the number of workers in $R(t,x)$. The cumulative exposure of worker ℓ at time t will be denoted by

$$z_{\ell}(t) = \sum_{j=I_{\ell}}^{t-G-1} d_{\ell j}$$

where $d_{\ell j}$ is the annual exposure for workers ℓ in year j , I_{ℓ} is the year of initial employment for worker ℓ , and G is a designated lag time. The various noncentral moments of the risk sets will be denoted by $\mu^{(k)}(t,x)$. That is,

$$\mu^{(k)}(t,x) = \frac{\sum_{\ell \in R(t,x)} z_{\ell}^k(t)}{N(t,x)}$$

The variance will be denoted by $\sigma^2(t,x)$ and the third and fourth cumulants by $K_3(t,x)$ and $K_4(t,x)$ respectively.

Let $\lambda(t,z,x)$ be the incidence rate or hazard at time t for a worker with exposure z . We then have $\lambda(t,z,x) = \lambda(t,x)(1 + \beta z)$ for the multiplicative linear model and $\lambda(t,z,x) = \lambda(t,x) + \beta_A z$ for the additive linear model where $\lambda(t,x)$ indicates the "spontaneous" risk and β (or β_A) is a measure of the size of the radiation effect. Implicit in this model is the assumption that the effect β (or β_A) is constant over some specified time period after exposure.

In general, the null hypothesis $H_0: \beta=0$ is tested by rejecting H_0 when a statistic Y exceeds y_α where y_α is chosen so that $P[Y > y_\alpha | H_0] \leq \alpha$. The power of the test for a particular value of β is given by $P[Y > y_\alpha | \beta]$.

A classical procedure for assessing mortality in an occupational setting is to compare the number of observed deaths with the number expected based on rates from a control population. The test statistic Y is the number of observed deaths, and is distributed as a Poisson variable with parameter

$$\sum_{tx} N(t,x) \lambda(t,x) [1 + \beta \mu(t,x)]$$

for the relative linear model and by

$$\sum_{tx} N(t,x) [\lambda(t,x) + \beta_A \mu(t,x)]$$

for the absolute linear model. The distribution of Y can thus be assessed by calculating the above quantities and then utilizing either tables of the Poisson distribution or its normal approximation.

In populations that exhibit substantial variability in exposure, procedures which utilize the exposure data can be expected to yield more powerful tests of significance than the approach described above. We consider an application of Cox's model which utilizes a direct comparison of doses without reference to an outside population. In this approach, which is described in the body of the paper, the test for $\beta = 0$ is regarded as a permutation test of $Z = \sum_{i=1}^n z_i(t_i)$ conditional on the risk sets R_i where i indexes the deaths due to a particular cause, t_i is the time (calendar year) of death for worker i , x_i denotes the stratum for worker i at time t_i , and $R_i = R(t_i, x_i)$. Asymptotically Z will be normal with mean $\sum_{i=1}^n \mu_i$ and variance $\sum_{i=1}^n \sigma_i^2$ where $\mu_i = \mu(t_i, x_i)$, $\sigma_i^2 = \sigma^2(t_i, x_i)$.

For the purpose of testing, it is appropriate to consider the conditional distribution of doses, but for the purpose of calculating the power of the above procedure, the occurrence of death must be considered as a random variable

which will be denoted by $\delta_\ell(t)$ where $\delta_\ell(t) = 1$ if death from cause of interest occurs for worker ℓ at time t , $\delta_\ell(t) = 0$, otherwise.

We are interested in evaluating the expectation and variance of the statistic

$$Y = \frac{Z - \sum_{i=1}^n \mu_i}{\left[\sum_{i=1}^n \sigma_i^2 \right]^{1/2}}$$

where $\sum_{i=1}^n \mu_i$ and $\sum_{i=1}^n \sigma_i^2$ will depend on the particular risk sets in which deaths occur and thus must be considered random variables. We will approximate the

mean and variance of Y by utilizing a first order Taylor series expansion of

$Y = u/v^{1/2}$ where $u = Z - \sum_{i=1}^n \mu_i = \sum_{tx} \sum_{\ell \in R(t,x)} [z_\ell(t) - \mu(t,x)] \delta_\ell(t)$ and

$v = \sum_{i=1}^n \sigma_i^2 = \sum_{tx} \sum_{\ell \in R(t,x)} \sigma^2(t,x) \delta_\ell(t)$. The required approximations are given by

$$E(Y) \approx E(u)/E^{1/2}(v) \quad \text{and}$$

$$\text{Var}(Y) \approx \frac{\text{Var}(u)}{E(v)} - \frac{\text{Cov}(u,v)E(u)}{E^2(v)} + \frac{\text{Var}(v)E^2(u)}{4E^3(v)} \quad (A1)$$

Because Cox's approach is based on the distribution of Z conditional on the risk sets, the $\delta_\ell(t)$ can be regarded as uncorrelated Poisson variables with parameters $\lambda(t,x)[1 + \beta z_\ell(t)]$. The needed expressions for equation (A1) above can be derived as follows:

$$\begin{aligned} E(u) &= \sum_{tx} \sum_{\ell \in R(t,x)} [z_\ell(t) - \mu(t,x)] \lambda(t,x) [1 + \beta z_\ell(t)] \\ &= \beta \sum_{tx} N(t,x) \lambda(t,x) \sigma^2(t,x) \end{aligned}$$

$$\begin{aligned}
 \text{Var}(u) &= \sum_{tx} \sum_{\ell \in R_{tx}} [z_{\ell}(t) - \mu(t,x)]^2 \lambda(t,x) [1 + \beta z_{\ell}(t)] \\
 &= \sum_{tx} N(t,x) \lambda(t,x) \{ \sigma^2(t,x) + \beta [K_3(t,x) + \mu(t,x) \sigma^2(t,x)] \}
 \end{aligned}$$

In a similar manner we obtain

$$E(v) = \sum_{tx} N(t,x) \lambda(t,x) \sigma^2(t,x) [1 + \beta \mu(t,x)]$$

$$\text{Var}(v) = \sum_{tx} N(t,x) \lambda(t,x) \sigma^4(t,x) [1 + \beta \mu(t,x)]$$

and

$$\text{Cov}(u,v) = \beta \sum_{tx} N(t,x) \lambda(t,x) \sigma^4(t,x) .$$

An alternative to analyzing individual doses is to categorize exposures and assign a score to each exposure group. Power for this approach, which is also described and illustrated in the body of the paper, can be calculated by replacing the individual doses by scores in the above formulae.