BNWL-SA-5992

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EVALUATING THE EFFECTS OF LOW-LEVEL CHRONIC EXPOSURES

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September, 1976

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FOLDER # 4 APRIL 1977 - DEC 1978

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INTRODUCTION

The general problem that I would like to discuss is that of assessing health effects of chronic low-level exposures to environmental contaminants. I will illustrate this problem with a particular study that I have been involved in for the past year and a half or so, namely a study of health effects of occupational exposure to ionizing radiation at Hanford.

Hanford was established in the early forties as an installation for plutonium production. Since this time, over 33,000 workers have been employed by the various AEC (later ERDA) contractors, many in jobs involving some exposure to radiation. Yearly records of this exposure, as well as occupational data, are maintained for all such employees. The yearly exposures are measured in rems of ionizing radiation able to reach critical organs of the body. Even for those who routinely work in radiation zones, yearly readings seldom exceed one or two rems.[1] This contrasts to other studies of radiation exposure where estimates of the effects of low-level exposure are based on linear extrapolation from data on single exposures of 100 rems or more. Our

[1] A Typical annual exposure from natural background radiation in the United States is about .1 rem. [10]

The recommendations of the National Council on Radiation Protection and Measurements (NCRP) [23] on occupational exposure to whole body penetrating radiation are that the accumulated exposure shall not exceed five rems multiplied by the number of years beyond age 18, and that the exposure in any calendar quarter shall not exceed three rems.

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interest is in assessing directly the health effects of continuing relatively small doses of radiation over a number of years. The methods considered should be applicable to evaluating exposures to other industrial and environmental contaminants.

Our information on health effects is limited to mortality data consisting of date, place, and cause of death. These data are obtained by having the Social Security Administration periodically search their records for deaths of previous Hanford employees. To ascertain cause, death certificates are then requested from the states where the deaths occurred. Some deaths are undoubtedly missed by this method and acquisition of certificates is a slow process which is never 100% successful. In addition to acquisition problems, mortality data present a number of other difficulties. Various biases may be involved in coding the cause of death. Since it is not practical to wait until everyone dies to analyze the data, our observations are truncated. Nonfatal health effects are of course missed completely.

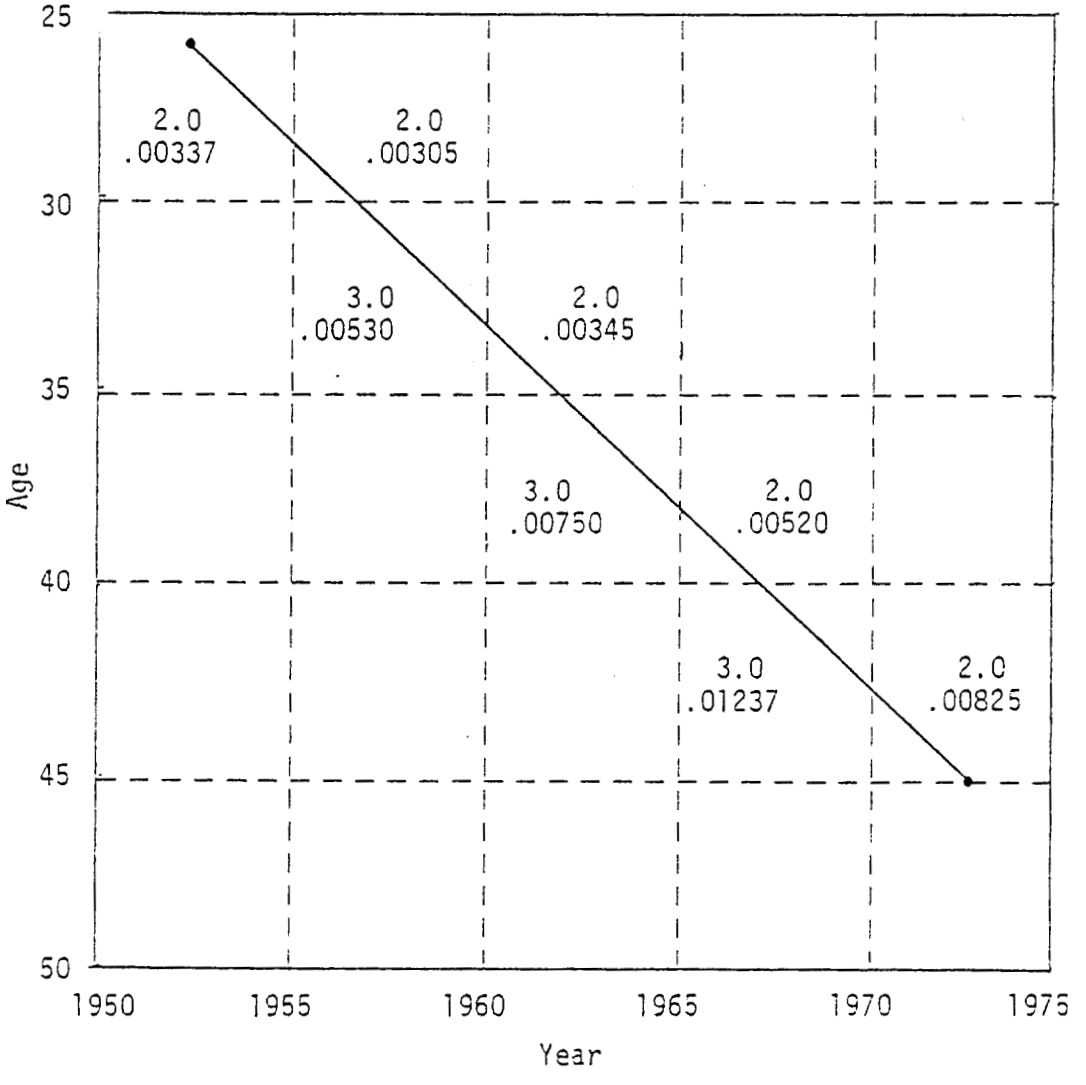
COMPARISON WITH VITAL STATISTICS

A classic method of analysis for occupational mortality studies is to compare death rates, both overall and cause-specific, with those of a control population, for example, all U.S. white males. The application of such a method involves calculating person-years in various age-calendar year categories, multiplying these person-years by the appropriate U.S. rates, and summing to obtain an expected number of deaths which can then be compared with the number observed.

For example, a person who initiates employment at Hanford on his 26th birthday at the beginning of 1953 and who survives until the end of 1971 (the cut-off point for the study) will have his person-years distributed as indicated in Figure 1. The first entry in each age-calendar year category indicates

FIGURE 1

Person-Years and Contribution to Expected Deaths of a Person Who Enters on His 26th Birthday at the Beginning of 1953, and Who Survives Until the End of 1971 (Cut-Off Point For the Study).



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person-years while the second entry is the individual's contribution to expected deaths. The latter is obtained by multiplying person-years by the corresponding age-calendar year specific death rate for U.S. white males. For example, the U.S. rate for 40-44 year-old white males between 1965-1969 is .004124 yielding a contribution of .004124 x 3.0 = .01237 expected deaths in this category. The total contribution for this individual is the sum of all such entries.

Richard Monson, at Harvard, has developed a computer program to carry out such calculations for 23 categories of cancer and 34 categories of other causes. The method is described in references [13] and [22].

An alternative to the population analysis described above is proportional mortality analysis in which one compares the distribution of deaths among causes with that of a control population. This method is simpler since information on the population at risk is not needed. It is especially valuable when such information is not available. The main limitation of this method is that there is no way of determining if an excessive proportion of deaths from one cause represents a true excess, or simply a deficiency of deaths from other causes.

At this point I will present a few results of the population analysis of the Hanford data. Table 1 shows the ratios of observed to expected deaths for a variety of causes. The numbers of observed deaths are given in parentheses. The ratio is known as the standardized mortality ratio or SMR. Results are given both for the total Hanford population (20,846[2] white males) and for those employed at Hanford for at least five years (10,236 white males). It is important to note that many short-term workers are included in the study, some who worked for as little as a week. Short-term workers are often omitted from occupational studies since they contribute little information about the effect

[2]Our analysis to date is limited to white males initiating employment prior to 1965. There are very few blacks and females with much potential for radiation exposure.

TABLE 1

Standard Mortality Ratios for All Hanford Workers and All Hanford Workers Employed for Five Years or More

(Number of Deaths is Given in Parentheses)

	All Workers	Workers Employed Five or More Years
Population at Risk	20,846	10,236
SMR* for		
All Causes	.79 (3394)	.75 (1331)
All Malignant Neoplasms	.85 (593)	.85 (265)
Cancer of Digestive Organs and Peritoneum	.87 (193)	.89 (87)
Cancer of Respiratory System	.85 (172)	.82 (79)
All Diseases of Nervous System and Sense Organs	.71 (222)	.69 (90)
All Diseases of Circulatory System	.81 (1460)	.77 (614)
All Respiratory Diseases	.86 (163)	.78 (65)
All External Causes of Death	.91 (403)	.77 (133)

*Cause specific SMR's are corrected for deaths with no cause information (7.1% for all workers, 3.5% for workers employed five or more years) on the assumption that the distribution of causes is similar for those with and without cause-of-death data.

of occupational hazards. To avoid bias from this omission, it is necessary to calculate person-years starting with the person's fifth anniversary of employment.

The total number of observed deaths among the Hanford population is only about 79% of what would be expected based on age-calendar year specific rates for U.S. white males. It is 75% of that expected for those spending at least five years at Hanford. This may appear impressive, but actually it is fairly typical for occupational studies. Employed persons are known to have lower death rates than nonemployed [21]. Hanford contractors provide yearly physical examinations for their workers, possibly postponing some deaths. And, of course, some deaths may be missed if no claim is filed with the Social Security Administration.

Biases resulting from comparison with U.S. rates can be reduced by calculating SMR's for various subgroups within Hanford and making internal comparisons. For example, we can compare long-term with short-term workers, the early cohort with later ones, workers with a potential for radiation exposure with those not likely to be exposed. The groups can be made as comparable as possible with respect to everything but the factor of interest. For example, since most of the occupations with a record of greater exposure are classified as craftsmen or operators,[3] an appropriate control might be craftsmen and operators in occupations with comparable pay, skill, and responsibility levels, but little potential for exposure.

Some results of this comparison are presented in Table 2. We see no evidence that the overall survival experience of those in occupations likely to be exposed has been adversely affected. Interestingly, the cancer SMR's at least up to 1972,

[3] Occupations were coded according to the standard occupational categories established by the Bureau of Census [1] with special codes introduced for occupations unique to the nuclear industry.

TABLE 2

Standard Mortality Ratios for Craftsmen and Operators with Five or More Years at Hanford

(Number of Deaths is Given in Parentheses)

	Craftsmen and Operators with a Potential for Radiation Exposure	Craftsmen and Operators Not Likely to be Exposed
Population at Risk	1844	1975
SMR for*		
All Causes	.65 (185)	.76 (316)
All Malignant Neoplasms	.92 (46)	.92 (68)
Cancer of Digestive Organs and Peritoneum	.94 (14)	.73 (17)
Cancer of Respiratory System	.88 (14)	1.09 (25)
All Diseases of Nervous and Sense Organs	.44 (8)	.71 (22)
All Diseases of Circulatory System	.67 (83)	.78 (148)
All Respiratory Diseases	.62 (8)	.91 (18)
All External Causes of Death	.65 (20)	.72 (26)

*In no case are the differences in SMR's statistically significant at the .05 level.

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are identical for the two groups. Note that less than 2,000 workers are in the potentially exposed group. If this group were not analyzed separately, adverse effects, if present, could easily be missed in the analysis of the total population. The comparison of the two groups presented above is limited in that our occupational data are difficult to categorize accurately, particularly for the many workers who held several different positions.

PROBLEMS IN ANALYZING TIME DEPENDENT VARIABLES

We now turn to the question of how best to deal with our dosimetry data. It might appear that these data could be handled by calculating the total penetrating dose for each individual and then comparing SMR's for employees in various exposure categories. However, because radiation exposure accumulates over time, we have a built-in bias; namely, the longer an individual lives the more opportunity he has to accumulate exposure. Or conversely, one way not to accumulate exposure is to die quickly.

To illustrate this phenomenon, suppose that all workers begin employment at age 25 in 1945 and accumulate exposure at the rate of 0.1 rem/year. We then have the results indicated below creating the illusion that exposure is conducive to long survival.

Age at Death	Total Exposure at Death
35	1 rem
45	2 rems
55	3 rems
65	4 rems

This problem is compounded by the fact that types of work involving possible radiation exposure expanded between about 1950 and 1965. In fact, of 2570 workers in our study with a total exposure of 5.3 rems or more, only 208 or about 8% terminated at Hanford before 1965 so that persons dying before then

did not have the opportunity to accumulate much exposure. This fact and the long latency period of many cancer types affect the interpretation of early analysis and accentuate the need for continued observation and frequent reanalysis.

The time-dependent nature of the data in low-level chronic exposure studies poses unique problems in analysis. In addition to the bias noted above, as an individual accumulates radiation exposure he may also be accumulating exposures to other agents or chemicals that may be incidental to his particular occupation. For example, most workers in radiation zones also receive some exposure to asbestos. Furthermore, since total exposure is clearly dependent on the number of years at Hanford, we can expect a correlation of exposure with factors such as participation in the medical surveillance program and residence in a relatively small desert community. Finally, the time and rate at which exposure is received requires careful consideration.

One method of handling the time dependency of our dosimetry data is to define two or more discrete exposure categories and then to allocate each worker's person-years according to his exposure status at the time. That is, a person is considered unexposed up to a time when he meets certain criteria. From then on he is categorized as exposed. One simple criterion might be that his total exposure exceeds a certain value. Since the years required for an individual to achieve the exposed status are counted as non-exposed years, these years do not bias the exposed group toward longer survival. The method can obviously be extended to handle more than two exposure states with a given worker possibly contributing person-years to several states. Of course, his death will occur in, at most, one state. A similar method is used by Newhouse [24] in his study of asbestos workers, although he allocates person-years on the basis of years of exposure rather than on a measure of the dose received.

On the basis of the above person-year allocation it is possible to calculate SMR's for the exposed and non-exposed states. A chi-squre test can be used to assess the statistical significance of any differences observed and the ratio of the two SMR's taken as a measure of the relative risk. However, as has been noted by Breslow [4], Yule [7], and others, there may be difficulties with this measure if the relative risk varies considerably for various age-calendar year categories.

DIRECT INTERNAL COMPARISONS: THE MANTEL-HAENSZEL STATISTIC

In the method above, age-calendar year specific rates for a control population (U.S. white males) are utilized for calculating expected deaths. This is not really necessary if our main concern is an internal comparison. Instead, we can compare death rates directly for each age-calendar year category and pool these comparisons for testing and for a summary measure.

Mantel and Haenszel [17] have developed such a procedure for the purpose of combining several 2 x 2 tables of the form

	Died	Survived	
Group I	r_{1i}	$N_{1i} - r_{1i}$	N_{1i}
Group II	r_{2i}	$N_{2i} - r_{2i}$	N_{2i}
	M_{1i}	M_{2i}	T_i

where i indexes strata for a variable such as age. Under the null hypotheses that there is no difference in death rates for the two groups, the expectations and variances of the r_{1i} conditional on the marginals are given by

$$E(r_{1i}) = N_{1i}\, M_{1i}/T_i \tag{1}$$

$$\text{and} \quad V(r_{1i}) = N_{1i}\, N_{2i}\, M_{1i}\, M_{2i}/T_i^2\,(T_i-1). \tag{2}$$

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If the death rates for the various strata are uncorrelated, the continuity-corrected statistic given below should be approximately distributed as chi-square with one degree of freedom

$$\chi^2 = \frac{\left(\left|\sum_i r_{1i} - \sum_i E\,(r_{1i})\right| - 1/2\right)^2}{\sum_i V(r_{1i})} \tag{3}$$

In the case of occupational data, the death rates r_{ji}/N_{ji} will generally be very small so that the r_{ji} can be regarded as Poisson variables. The finite correction factor, M_{2i}/T_i-1, in equation (2) will be very close to one and can be omitted, resulting in

$$V(r_{1i}) = N_{1i}\ N_{2i}\ M_{1i}/T_i^2 \quad . \tag{4}$$

In this situation, the N_{ji} may be replaced by the number of person-years, t_{ji}, in the ith strata group j. The r_{ji} are still Poisson and formulas (1), (3), (4) and (5) apply. The "survived" column in the above table will have no meaning. (See Armitage [28]).

There are a number of possibilities for summary measures of relative risk. The two presented below are respectively the ratios of standardized rates based on the "direct" and "indirect" methods, where the standard population is taken to be the pooled exposed and nonexposed populations.

$$R_1 = \frac{\sum_i r_{1i}\ T_i/N_{1i}}{\sum_i r_{2i}\ T_i/N_{2i}}$$

$$R_2 = \frac{\sum_i r_{1i}/\sum_i Er_{1i}}{\sum_i r_{2i}/\sum_i Er_{2i}} \quad . \tag{5}$$

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The relative merits of these and other measures are discussed by Mantel and Haenszel [17] and by Breslow [4].

Mantel [18] has extended his results in a number of directions, including the case in which several groups, possibly ordered, are being compared. The application of his method to censored survival data is discussed in reference [19].

Other variables of importance such as years from initial employment at Hanford, years employed at Hanford, and work cohort can be handled by introducing additional strata into the model, either with or without the use of U.S. vital statistics. Since the Mantel-Haenszel procedure requires only that the sum of the exposed deaths have a normal distribution, the size of individual strata can be quite small. However, there is some limit since a stratum will contribute nothing if any of the marginals N_{1i}, N_{2i}, M_{1i} are zero. If vital statistics are used to adjust for age and calendar year, it is probably possible to stratify more finely on other variables.

DOSE-RESPONSE RELATIONSHIP OVER TIME

We now turn to the question of the relationship of any effects with the time that has passed since exposure. This is a complex question since if one assumes that there are multiple stages (initiating and promoting) in the genesis of cancer, early exposure may affect a different stage than later exposure.

One possibility for handling the problem is to introduce latent periods of various lengths into the definition of the exposed state. For example, an individual could be considered exposed only after surviving ten years past the accumulation of a given total exposure.

Another alternative is to treat the interval from exposure as yet another stratum. The problem here is that the stratum is defined only for those in the exposed table. If the same control (from the nonexposed table) is used for each such exposure interval group, our final resulting chi-square statistic is obtained by summing over correlated comparisons. Thus the test is of dubious validity. However, for descriptive purposes, this procedure may still provide a valuable tool for gaining insight into the nature of any possible relationship.

The procedure above was originally suggested by Mantel and Byar [20] for analyzing heart transplant data. In their study, receiving a transplant is analogous to entering the exposed group; while being accepted as a candidate for surgery corresponds to initiating employment at Hanford. As a way out of the difficulty encountered above (i.e., correlated comparisons), they suggest comparing later exposure with earlier exposure. For example, nonexposed person-years could be compared with exposed person-years; the first five years after exposure could be compared with later experience; and the next five years compared with still later experience, etc. Such comparisons can be shown to be uncorrelated and the resulting chi-square valid. This analysis addresses the question of the comparison of earlier versus later exposure.

There are certainly many other possibilities for utilizing the available dosimetry data than those discussed above. In particular, further consideration should be given to the choice of the procedures that will be most meaningful in handling the time relationship with more than two exposure states considered.

COX'S CONDITIONAL MODEL

Before closing, I briefly consider Cox's conditional model for survival with concomitant variables. This model, introduced by D. R. Cox in a key paper in 1972 [5], offers almost unlimited possibilities for more elaborate analysis

and includes as special cases the methods proposed thus far.

Suppose that each individual in our study has measurements $z_1,\ldots,z_p$ where these may be measurements of primary interest such as radiation exposure, or concomitant variables that need to be accounted for, such as years at Hanford. The variables may be time dependent.

Cox defines his basic model in terms of a <u>hazard function</u>. The hazard function can be thought of as the instantaneous risk of dying (or failure of some type). Cox makes the assumption that the hazard $\lambda(t,\underline{z})$ is of the form

$$\lambda(t,\underline{z}) = \exp\,(\underline{z}\underline{\beta})\lambda_0(t) \tag{6}$$

where t denotes time either from birth (i.e., age) or from onset of the study (initial employment at Hanford), $\underline{z} = (z_1,\ldots,z_p)$ and $\underline{\beta}' = (\beta_1,\ldots,\beta_p)$. Note that no assumptions are made about the hazard function $\lambda_0(t)$. The assumption involves only the manner in which $\underline{z}$ affects survival.

Cox then proceeds to argue conditionally on the particular times that deaths occur. Suppose that $t_{(i)}$ is the set of all individuals alive and at risk of dying at time $t_{(i)}$. Then, arguing conditionally on the risk set $R_{t(i)}$, the probability the death is on the individual as observed is

$$\frac{\exp\,(\underline{z}_{(i)}\underline{\beta})}{\sum\limits_{\ell\varepsilon R_{t(i)}} \exp(\underline{z}_{(\ell)}\underline{\beta}} \tag{7}$$

The product of the above expressions over all deaths can be treated as a likelihood function. That is, the logarithm can be differentiated, and the resulting equations solved iteratively to obtain estimates of $\underline{\beta}$.

Cox's model carries out the finest stratification possible on the basic time variable, t, with just one death per stratum. It is possible to group data on this variable (see reference [3], [15], [25]) and then stratify as well on

additional variables. The special case in which there is a single binary concomitant variable, z_1, leads to the test proposed by Mantel [19] above. The case in which a single variable takes on multiple values, or even a continuum of values, leads to the same tests as Mantel's extensions in this direction [18]. However, in addition, Cox's model provides estimates of the coefficient β which can be interpreted as the logarithm of the relative risk.

If the variable t is taken as time from initial employment at Hanford, vital statistics can be incorporated into the model as a means of handling age and calendar year.

Cox's model offers potential for handling several measures of radiation exposure simultaneously as well as an alternative procedure for handling concomitant variables such as years at Hanford. One might for example, define t as the time from accumulation of a certain total dose and utilize prior and subsequent experience as concomitant variables. Crowley and Hu [7] discuss the use of Cox's model with time dependent variables and use it to analyze heart transplant data.

The results of analyses based on Cox's model with several time dependent variables may be difficult to interpret. Certainly the validity of the basic assumption that $\lambda(t,\underline{z}) = \exp(\underline{z}\beta)\lambda_0(t)$ needs to be evaluated carefully.

SUMMARY

Hopefully this presentation has raised questions worthy of further comment and discussion. I would propose the following questions for your consideration:

(1) How does one interpret the comparison of the mortality experience of Hanford workers with an outside control population (for example, all U.S. white males)? I feel that such a comparison tells us very little about the possible effects of radiation exposure, but does it give us other important information?

Is there an alternative control which would be more appropriate? What should be the role of proportional mortality analysis?

(2) When making internal comparisons, how should one handle the critical variables, age and calendar year? Should rates from a control population be utilized for this purpose, or should comparisons be made directly using a procedure such as that devised by Mantel and Haenszel? What are the best measures of relative risk using either method?

(3) How should other concomitant variables (such as years at Hanford, occupation, cohort) be handled? Methods which have been considered are restricting the analysis to certain relevant subgroups, stratification with a summary test and measure, and Cox's regression model.

(4) How should the dosimetry data be handled? What are the most relevant facts about radiation exposure? How can insight be gained into the nature and magnitude of the dose-effect-time relationship (if such a relationship is present)? Such methods as allocating person-years by exposure states, comparing various time periods after exposure, and Cox's regression model may prove useful.

ACKNOWLEDGMENTS

I would like to thank Dr. Norman E. Breslow and Dr. Edward B. Perrin for many helpful comments on this topic, and Dr. Sidney Marks for suggestions leading to several improvements in the final wording of this paper.

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