An Exposure-Time-Response Model for Lung Cancer Mortality in Uranium Miners: Effects of Radiation Exposure, Age, and Cigarette Smoking

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Abstract. This report describes the exposure-time-response model developed in 1969-1970 in an attempt to improve estimates of long-term risk from lung cancer mortality attributable to mining uranium (1-2). Also reported are results of the later use of the model to study the risk of mortality from lung cancer as it relates to level of cigarette smoking, age, and radiation exposure (3). A ten-year median lognormal distribution of the latent period between induction and death predicted the observed time and age of death from lung cancer except for an excess of observed in the 45-49 year age group. The risk increased progressively from nonsmokers to light to heavy cigarette smokers. However, the excess risk over that for non-miners with equivalent smoking levels was much less for nonsmokers but was about the same for light and heavy smokers. It is suggested that smoking at both levels promotes (hastens the appearance of) lung cancer induced by radiation and that the excess risk for nonsmokers will increase.

Introduction. The United States uranium miner study and the related metal miner study pioneered useful methodologies for analysis of cohort studies (4-8). Notable features are the display of lung cancer mortality by time interval following first exposure in underground uranium mining and by level of cumulative radiation exposure. Despite the availability of these methodologies, when it became necessary to evaluate the long-term implications of proposed standards for airborne levels of radiation in mines a methodologic problem arose. Because exposure occurred over time so that the time of induction or initiation of cancer was unknown, adjustment for the latent period between induction and death from lung cancer

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was not possible. It was known that the lower cumulative exposure groups were not followed as long as the higher exposure groups, partly because many miners accumulated sufficient additional exposures to move them into higher groups and partly because of the downward temporal trend in mine radiation levels. Additional reasons for devising improved methods were to obtain estimates of lung cancer risk which did not change with calendar time as had those using the previous method (7), to more adequately study and control for the effects of age and to evaluate the possibility of an exposure-rate effect.

In this paper several hypotheses concerning the relation between radon daughter exposure and excess lung cancer risk are formulated and tested.

1 The excess risk for a miner over that expected for his age is proportional to a function of his past radiation exposure (absolute risk hypothesis).

2 The excess risk for a miner is proportional to the product of his expected risk times a function of his past radiation exposure (relative risk hypothesis).

3 The latent period between induction of and death from lung cancer is 5, 10, or 15 years.

The test criteria for these hypotheses are whether they predict the actual temporal distributions of lung cancer deaths by age, calendar time and years after start of underground uranium mining. The hypotheses which are not rejected are then used in a computational

model to evaluate the nature of the relation between risks from exposure to cigarette smoke and airborne radiation.

Methods. From 1950 through 1960 medical examinations were offered periodically to uranium miners in Arizona, Colorado, New Mexico and Utah (four state area). Before 1954 no attempt was made to examine all miners, but starting with 1954 as many miners as possible were examined. In 1957 and 1960 approximately 90% of uranium miners working in the areas surveyed were examined.

The present report concerns the 3,366 white men who had been examined at least once and who mined uranium underground for at least one month before January 1, 1964. Follow-up was carried out from the date of their first examination through September 30, 1968, the termination date for this analysis. Non-white miners were not studied because at that time they had too few respiratory cancer deaths. Less than 1% of the men were lost to observation. Many techniques of follow-up were used, the commonest being an annual census of uranium miners, mail questionnaires and records of the Social Security Administration.

Copies of death certificates were obtained for individuals who died. The underlying cause of death was coded by a trained nosologist according to the sixth revision of the international lists of diseases and causes of death.

In order to quantify the amount of radiation exposure for each miner we needed to know in which mines and at what times he worked, as well as the radiation levels for those mines and times. Mine

employment histories were obtained at the time of the survey examinations, annual uranium miner censuses, and from mail questionnaires. Details of the coding procedures and assessment of the quality of the histories have been recorded elsewhere (2). Radiation levels were quantified by reducing nearly 43,000 radiation measurements to annual averages or estimates of radon progeny levels for each of the nearly 2,500 uranium mines in the study. These annual estimates were expressed in working levels (WL) which are defined as 1.3×10^5 MEV of potential alpha energy per liter of air from any mixture of radon progeny. The cumulative amount of radiation exposure was calculated for each miner starting with the date of his first underground uranium mining and ending with his last month at risk of dying in this study. This estimate of radiation exposure was expressed as cumulative working level months (WLM) which is defined as that exposure received by a worker exposed to an atmosphere of 1 WL for 173 hours. WLM estimates are the product of underground exposure during specific "working months," or fractions thereof, and the concentration of radon progeny in working levels specific for mine and year.

Smoking histories obtained at the last survey examination for each miner were used to define cohorts by level of cigarette smoking as follows: a) non-cigarette smoker; b) former cigarette smoker; c) light smoker (one pack or less daily); and d) heavy smoker (more than one pack of cigarettes daily).

A modified life table technique (5) was used to obtain person-years at risk of dying for cigarette smoking cohorts, or other

subgroups of interest, cross-classified by single calendar year, by five year age group, by five year intervals of time after start of underground uranium mining, and by estimated WLM group. Because smoking specific rates were not available for men under 35, only person years for older miners were used in the smoking analysis. In addition, average effective WLM (a weighted exposure index to be described in the next section) was calculated for the person-years at risk in each subgroup of interest.

Comparisons with the general population of white males were made by noting the observed number of lung cancer deaths among the miners in relation to an expected number. This expected number was calculated in two ways in this report. In the first part age and year specific respiratory cancer rates (international list numbers 160-164) for the general population of white males living in the four-state area were used. In the second part United States white male lung cancer rates (international list numbers 162-163) specific for age, calendar year and cigarette-smoking category were used. In both parts the specific rates were multiplied by the appropriate number of person-years at risk to obtain the expected numbers.

The Model. Measures of excess lung cancer risk are dependent upon person-years at risk of dying. Thus the problem is viewed as one of estimating the radiation exposure which is effective in the production of (or is responsible for) the excess risk during a particular calendar year; i.e., an appropriate exposure unit is being sought. The new weighted exposure index estimates effective WLM under

certain assumptions. It takes into account the time between each calendar year of radiation exposure and each calendar year at risk of death as well as the level of WLM exposure in each preceding calendar year. (The concept is related to the "equivalent dose" in the report on radiation-induced leukemia among patients with ankylosing spondylitis (9).) To estimate effective WLM it is assumed that the latent period (i.e. time between induction and death) for lung cancer mortality had the same-shape and dispersion, but not necessarily the same mean as that for leukemia following single exposure to radiation and as the incubation period of infectious diseases. Specifically assumed are: 1) a log normal distribution of time of lung cancer death following a single exposure with a standard deviation of 0.17609 in log t units, where t = years after exposure; and 2) that the increased risk from subsequent exposures can be added to the risk from earlier exposures. The latter assumption is consistent with the one-hit model of cancer induction. To the extent which the data permit, the effects of exposure rate, cumulative exposure, and age at first exposure are evaluated by making certain assumptions and then comparing how well the predicted distributions of deaths fit the observed.

These assumptions motivated the definition of Effective WLM(k) in year k as

$$\text{Effective WLM}(k) = \sum w(k-j)\ \text{WLM}(j) \qquad 0 < j < k$$

where w(k-j) is that proportion of the area under the lognormal density curve which is bounded by the interval from k-j - ½ years to k-j + ½ years, and where WLM(j) is the exposure in WLM during year j.

In subsequent analyses, an average effective WLM is determined for each level of each variable of interest; e.g., age, calendar time, years after start of underground uranium mining, smoking category, etc. The first of two hypotheses to be examined concerning the specific type of response is that the increase in absolute risk is proportional to the level of radiation exposure. This model implies that the increase in rate is independent of (i.e., can be added directly to) the rate associated with other causes such as cigarette smoking, environmental factors, and aging. An alternative hypothesis is that the increase in relative risk is proportional to the level of radiation exposure. That is, that the increase in risk is proportional to that risk which would have characterized the miners in the absence of radiation.

In examining each of the above hypotheses, predictions from the computational model were contrasted with temporal distributions of lung cancer deaths. Predictions were made for the 3 temporal variables of the life table: (a) age, (b) calendar time, and (c) years after start of underground uranium mining according to the following models:

1) Absolute risk hypothesis: predicted number n_x of excess lung cancer deaths among those in stratum x is proportional

to the average effective WLM_x in the stratum, where average effective WLM_x is averaged over all person-years in the stratum:

$$n_x = \alpha_A \text{ (average effective } WLM_x).$$

2) Relative risk hypothesis: predicted excess number n_x is proportional to the product of the expected number E_x of cancers in the stratum times average effective WLM_x:

$$n_x = \alpha_R E_x \text{ (average effective } WLM_x).$$

The constants α_A and α_R were estimated by equating the total predicted and observed number of lung cancer deaths. Here "total deaths" refer to deaths cumulated over all strata x.

Predicted excess number of lung cancer deaths was added to the expected number to obtain the total predicted number of lung cancer deaths for a particular level of the temporal variables a, b and c. Age and smoking adjustments were made by using age or smoking category specific proportionality constants α to calculate the predicted number of excess deaths according to the variable of interest. These predicted numbers were then added over all ages or smoking categories.

Findings with Regard to Temporal Variables. Figure 1 shows that for each of the three median latent periods the absolute risk hypothesis predicted far too many deaths among miners under 45 years of age. The relative risk hypothesis gave results much closer to those observed. It may be seen that the 10 year median latent period assumption is consistent with observed data with the exception of an excess observed in the 45-49 year age group balanced by a deficit observed in the 60-64

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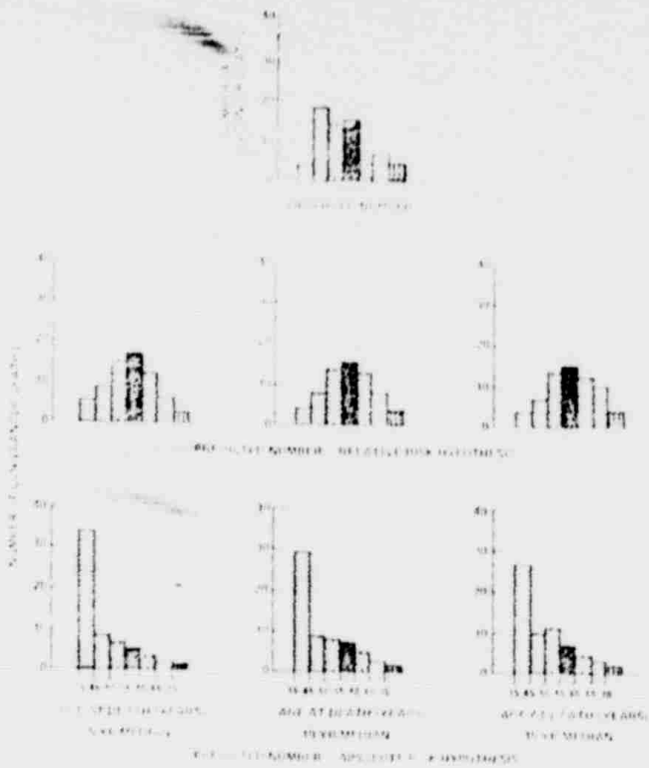


Figure 1

year age group. Figure 2 shows that both 10 and 15 year median latent period relative risk hypotheses gave reasonably good fits to the deaths arranged by calendar period of death. The 10 year median relative risk hypothesis gave the best fit by time after beginning of underground uranium mining and was chosen to use for additional analyses because it

gave the best overall fit to the temporal variables. The data available for this analysis were those through September 1967 (1).

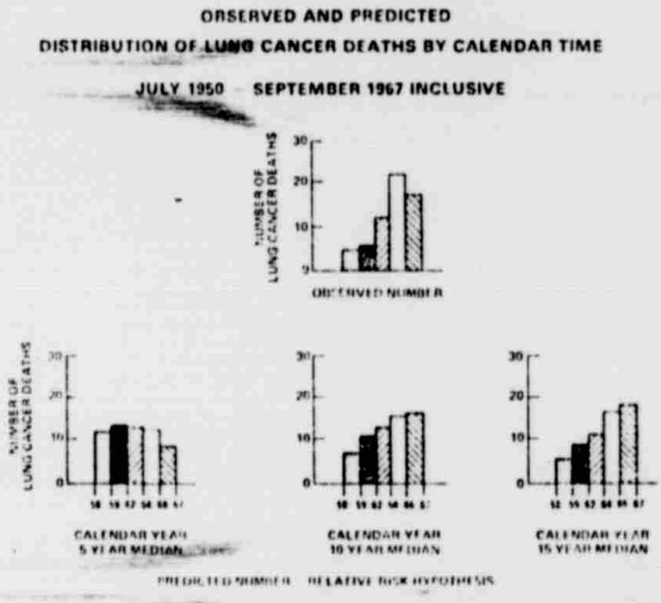


Figure 2

The effect of age at start of exposure on lung cancer mortality was also evaluated using this model. After adjustment for age at risk there was good fit indicating no effect of age at initial exposure over and above that related to age at death. The effect of calendar time period of first exposure was also explained by the model in that predictions fit the observed distributions (2).

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In order to evaluate whether or not there is an exposure-rate effect, the white underground miners who were alive on October 1, 1960 were divided into 3 cohorts on the basis of estimated average WL of exposure in uranium mines prior to that date. After adjustment for WLM category it was concluded that insofar as these data permitted, the risk was not dependent on exposure-rate per se (2).

Cigarette Smoking. Earlier reports from the United States Public Health Service epidemiologic study of uranium miners have shown that 1) the excessive lung cancer mortality could not be explained by cigarette smoking alone (8) and 2) that lung cancer experience varied systematically with radiation exposure and that adjustment for smoking had very little effect on the observed exposure-response relationship (6).

Findings with Regard to Smoking and Age. In Table I the data are classified according to time after start of underground uranium mining. The first column shows person-years at risk of dying during this study. These were multiplied by general population rates for the appropriate age, year, and smoking class to get the expected deaths in the second column. For each category except the first, observed deaths greatly exceeded the expected number.

TABLE 1 Expected*, observed and predicted distributions of lung cancer deaths and average effective working level months by years after start of underground uranium mining, October 1960 through September 1968

Years after start of underground uranium mining	Person-years at risk	Distribution of lung cancer deaths				Average Effective WLM**
		Expected*	Observed	Predicted		
				Not adjusted for smoking	Adjusted for smoking	
Less than 5	1,272	0.78	1	0.85	0.84	1.614
5-9	5,539	4.65	10	10.86	10.58	26.378
10-14	5,737	5.87	23	25.42	24.68	65.876
15-19	1,952	2.02	15	10.71	11.25	84.798
20-24	1,211	0.93	6	4.58	5.45	77.400
25 and over	1,163	1.26	7	9.59	9.20	64.312
Total	16,878	16.51	62	62.01	62.00	50.983

* Based on indirect standardization for age, calendar year, and smoking category.

** Effective WLM averaged over individuals in the stratum weighted by their person-years and based on estimated WLM exposure in uranium mines only.

In the fourth column the predicted distribution of the 62 lung cancer deaths is based on the 10 year median relative risk hypothesis. The 45.5 excess deaths (that is total observed minus total expected) were allocated in direct proportion to the product of average effective exposure (last column) times the expected number (second column). These allocated deaths were then added to the expected number to obtain the unadjusted predicted number. Adjustment for smoking was made by distributing the excess number of lung cancer deaths within each of the four smoking classes, adding them to the expected number and adding the resultant predicted numbers over the four smoking categories. This adjustment didn't change the predicted numbers very much. Note the close fit of observed and predicted numbers. We conclude that this model, by taking account of latency and amount of radiation, was a good predictor of the time of occurrence of the lung cancer deaths.

Table 2 is similar in format to Table 1, except that age has been substituted for time elapsed since start of mining. Age specific data have not been presented earlier because it was felt necessary to consider both latent period and amount of radiation before they could be interpreted. Again, the observed and predicted numbers of lung cancer deaths are similar; however, there were 16 observed vs. 6 predicted for the 45-49 year age group and a deficit of observed deaths in the 65-69 year age range. The age patterns of observed vs. predicted numbers are similar for light vs. heavy smokers.

Table 3 presents the main findings of this analysis. The data are shown for the 3 smoking classes rather than in relation to a tim scale. There are important differences between light and heavy smokers. Light smokers (one pack or less daily) had 5.9 times the expected number of lung cancer deaths as compared to only 1.3

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times the expected number for heavy smokers. Another way to see this difference is to compare the observed numbers with the first column of predicted numbers. Note that the predicted number computed in the usual way from the expected number was lower than observed for light smokers and that it was higher for heavy smokers. The relative risk hypothesis must be rejected.

If the radiation-related excess does not depend on the expectation due to smoking, could it depend upon that expectation characteristic of non-smokers? The second column of predicted numbers addresses this question. For non-smokers themselves the answer was no, only 2 deaths were observed whereas 11 were predicted.

Table 3 also has another column from which non-smokers were omitted and the 60 deaths in smokers were redistributed, again using expected numbers derived from nonsmoking rates. Using this model, light and heavy smokers appeared to have similar excess lung cancer risks. Please note that this model, which was based upon non-smoking rates, did not fit the non-smokers themselves.

In Table 4 lung cancer rates for the four smoking classes are shown. The three estimated components add up to the total observed rates. The lung cancer deaths attributed to mining or radiation were estimated from the excess of observed over expected numbers. Those with a non-smoking non-mining etiology were estimated by an expected number calculated from non-smoking rates for the general

population and the component attributed to smoking was obtained by subtraction of these from the expected number derived from age and smoking category specific U.S. lung cancer rates.

TABLE 4 Observed number of lung cancer deaths, total rates and estimated rates for non-smoking non-mining, smoking and mining effects by cigarette smoking classification, October 1960 through September 1968

Cigarette Smoking Classification	Number of Lung Cancer Deaths	Rates per 10,000 person-years			
		Observed	Estimated Components		
			Non-smoking Non-mining*	Smoking**	Excess over Expected ***
Non-smokers	2	6.5	1.7	0	4.8
Former smokers	5	42.1	1.9	0.7	39.5
Smokers of ≤ 1 pack daily	18	41.0	1.3	5.7	34.0
Smokers of > 1 pack daily	17	51.2	1.1	26.6	23.4
Total	42	36.7	1.4	8.4	27.0

* Based on non-smoking rates specific for age and calendar year.

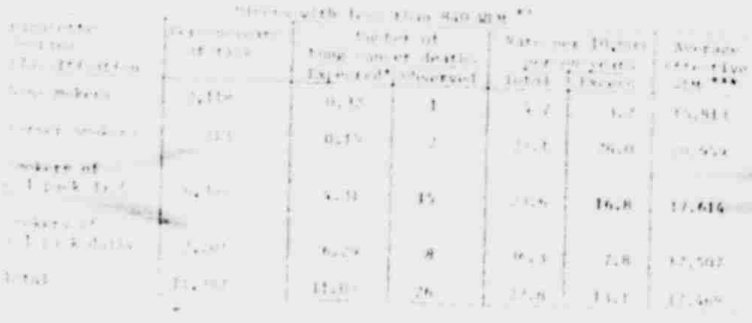
** Based on indirect standardization for age and calendar year minus non-smoking rates.

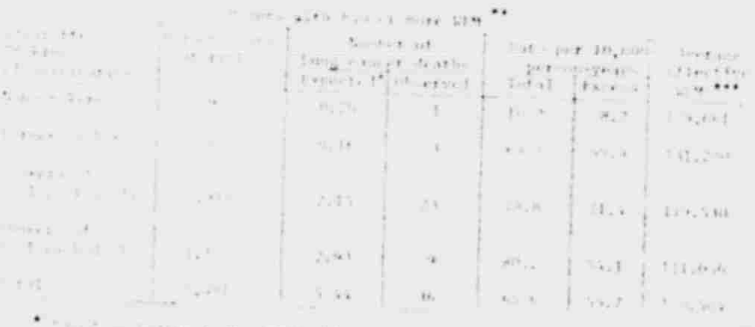
*** Based on excess of observed rates over expected rates standardized for age and calendar year.

Non-smokers had lower total and excess rates than smokers. The total rate for heavy smokers was the highest in the Table. However, the excess rate attributed to mining or radiation was higher for light than for heavy smokers, the opposite of what would be expected if uranium mining and cigarette smoking acted synergistically.

In Table 5 the data are divided into 2 parts, depending on whether or not the one part had less and the other had associated cumulative exposure exceeding 840 WLM. Total and excess rates are shown near the

right side of the table. The pattern of rates is like that in Table 4 and in addition show the effect of the different levels of WLM of exposure. The excess of lung cancer deaths is seen for light as compared to heavy smokers in both cumulative exposure groups but particularly in those with less than 840 WLM.





Discussion of Cigarette Smoking and Radiation. The effects of simultaneous exposures of man to industrial pulmonary carcinogens and tobacco smoke have been variously interpreted in terms of the nature of the interrelationship. Tobacco smoke is a complex mixture of substances containing both initiators and promoters of cancer. It might act in either or both of these ways. Determination of the nature of the interrelationships is of more than academic interest. For instance, if the excessive bronchogenic cancer rates observed are mainly synergistic (i.e. greater than the sum of the two separate effects), then rates could be greatly lowered simply by avoiding either one of the interacting agents -- whichever is easier to avoid. If, however, the excessive rates are mainly the result of additive effects of two carcinogens or if either acts as a promoting as well as an initiating agent, then prevention would require avoidance of both agents because even without promotion the cancers would occur later.

This report has attempted to attribute the excess lung cancer risk noted among uranium miners to different etiologic factors so that the interaction could be examined more closely. This was done by concentrating on that lung cancer which is in excess of expectation at general population rates.

The two major findings with regard to cigarette smoking are 1) light and heavy smokers had approximately the same levels of radiation-induced lung cancer and 2) non-smokers had a much lower level of radiation-induced lung cancer. These findings (Table 3), when

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consistent with earlier findings, are consistent with 2 hypotheses: I) lung cancers are initiated by irradiation, independently of cigarette smoking, and II) cigarette smoking promotes the development of the lung cancers initiated by radiation. Heavy smoking seems to initiate many more cancers than light smoking, but both levels of smoking have a powerful promoting effect on cancers initiated by radiation.

If smoking acts as a cancer promoter as this study suggests, one would expect that the latent period for non-smokers would be longer than that for smokers and that eventually the excess risk for non-smokers may approach that for smokers. In agreement with this possibility are the facts that the lifetime lung cancer risk of Schneeberg miners was quite high during a period before cigarettes came into use and that lung cancer is now becoming much more common among the Indians in our study who smoked very little (9).

Whatever the possible effects on radiation-induced lung cancer of changes due to smoking, it seems clear that the squamous metaplasia and atypical cells thought to be involved in tobacco-induced lung cancer, do not provide a simple explanation for the greater suspectibility of smokers to radiation-induced lung cancer. This is because these changes are highly smoking-dose-correlated whereas the susceptibility to radiation-induced lung cancer is not. These changes could, however, also be produced by the radiation.

Because data on the smoking habits of the population were not available for the four-state area it was necessary to use rates for the entire United States. These rates and the expectations which they generated

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are thought to be too high because the Standardized Mortality Ratio (SMR) for the four-state area was only 76 (5). The effect of this presumed bias would be to underestimate the excess lung cancer for all groups; however, groups which have a large expectation relative to their total of observed deaths (such as smokers of more than one pack daily) would be most affected. Correction for this bias would make the excess rates for the light and heavy smokers more alike; i.e., might reduce the difference of 10 per 10,000 person-years down to 5 per 10,000 person-years.

Since the data for this study were collected and analyzed, new data from this and other studies of miners have been reported. One of the authors (VEA) interprets this more recent literature as indicating that a number of factors such as exposure rate, age at exposure and age at death do influence lung cancer risk from airborne radiation and should be incorporated into an absolute risk model to improve the predictability of the work reported here. It would appear that a longer median latent period will be required to fit the data for non-smokers. The extent to which these and other factors influence the distribution of lung cancer risk attributable to airborne radiation can only be determined by further modelling of observed data. Similarly, longer term follow-up will be required to establish or refute the validity of the shape of the assumed model response curve, particularly its later part.

Summary. An exposure-time-response model for estimation of long-term risk from airborne radiation has been described. Assuming a

relative risk model plus a lognormal distribution with a 10 year median latent period between lung cancer induction and death, the temporal distribution of excess lung cancer in the study group of white United States uranium miners was predicted. An important exception to the good fit of the data was the 15-19 year age groups which experienced a large excess over that predicted.

When the relationship between cigarette smoking and radiation exposure was studied with the above exposure-time-response model it was found that 1) cigarette smokers had a much greater lung cancer mortality from radiation than did non-smokers and 2) this excess mortality had approximately the same magnitude for light and heavy smokers; i.e., did not depend on the risk from level of smoking. Interpretations and implications of these findings were discussed.

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REFERENCES

(1) F.E. LUNDIN, Jr., J.W. WAGONER and V.E. ARCHER, Public Health Service Uranium Miner Report to National Academy of Sciences, National Research Council, Division of Medical Sciences, Ad Hoc Advisory Committee to the Federal Radiation Council, Bureau of Occupational Safety and Health, DHEW, Salt Lake City, Utah, 1970.

(2) F.E. LUNDIN, Jr., J.W. WAGONER and V.E. ARCHER, Radon Daughter Exposure and Respiratory Cancer, Quantitative and Temporal

Aspects, U.S. Dept. of Health, Education and Welfare, Public Health Service, National Institute for Occupational Safety and Health, National Institute of Environmental Health Sciences, Joint Monograph No. 1, Springfield, VA, National Technical Information Service, U.S. Dept. of Commerce, 1971.

(3) F.E. LUNDIN, Jr., V.E. ARCHER and J.K. WAGONER, Lung Cancer Mortality of Uranium Miners in Relation to Cigarette Smoking, Age and Radiation Exposure, October 1960 through September 1968, read before the special session on "Epidemiological Contributions to Environmental Health Policy," Annual Meeting of the American Public Health Association, Atlantic City, New Jersey, November 14, 1972.

(4) J.K. WAGONER, R.W. MILLER, F.E. LUNDIN, Jr., J.F. FRAUMENI and M.E. HAIJ, Unusual Cancer Mortality Among a Group of Underground Metal Miners, New. Eng. J. Med. 269(1963), pp. 284-289.

(5) J.K. WAGONER, V.E. ARCHER, B.E. CARROLL, D.A. HOLIDAY and and P.A. LAWRENCE, Cancer Mortality Patterns Among U.S. Uranium Miners and Millers, 1950 through 1962, J. Nat. Cancer Inst. 32(1964), pp. 787-801.

(6) J.K. WAGONER, V.E. ARCHER, F.E. LUNDIN, Jr., D.A. HOLIDAY and J.W. LLOYD, Radiation as the Cause of Lung Cancer Among Uranium Miners, New. Eng. J. Med. 273(1965), pp. 181-188.

(7) F.E. LUNDIN, Jr., V.E. ARCHER, E.M. SMITH and J.K. WAGONER, Lung Cancer Among U.S. Uranium Miners; Current Assessment of Risk, read before the Epidemiolgy Exchange of American Public Health Association, Miami, Florida, October 24, 1967.

(8) F.E. LUNDIN, Jr., J.W. LLOYD, E.M. SMITH, V.E. ARCHER and D.A. HOLIDAY, Mortality of Uranium Miners in relation to Radiation Exposure, Hard Rock Mining and Cigarette Smoking - 1950 Through September 1967, Health. Phys. 16(1969) pp. 571-578.

(9) W.M. COURT-BROWN, and R. DOLL, Leukemia and Aplastic Anemia in Patients Irradiated for Ankylosing Spondylitis, Med. Res. Counc. Spec. Rep. (London) 295(1957), pp. 1-135.

(10) V.E. ARCHER, J.D. GILLAM, and J.K. WAGONER, Respiratory Disease Mortality Among Uranium Miners. In Occupational Carcinogenesis, SAFFIOTTI, U. and WAGONER, J.K. (ed.) New York Academy of Sciences, New York, New York, 271(1976), pp. 280-293.