Modeling Occupational Mortality Data With Applications To U.S. Uranium Miners

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Approved by:

[Signatures of advisors and readers]
ABSTRACT

RICHARD WILLIAM HORNUNG. Modeling Occupational Mortality Data with Applications to U.S. Uranium Miners. (Under the direction of Michael J. Symons.)

The development of Statistical methodology for application to survival data has expanded rapidly in the last two decades. Increasing interest in the field of occupational health demands that the current state-of-the-art in modeling exposure-risk relationships be utilized in assessing potential dangers to worker health. It is the aim of this research to investigate the more sophisticated survivorship models in producing a quantitative risk assessment of lung cancer in U.S. uranium miners.

The Cox proportional hazards model was chosen for this purpose. A variety of risk functions are examined, with a power function model providing the best fit. A number of risk factors influence the exposure-response relationship. Among these are a strong independent multiplicative effect of cigarette smoking, a positive effect for age at initial exposure, and a negative effect for time since last exposure. The nature of the temporal effects suggest that exposure acts at a late stage (promoter) in a multistage carcinogenesis model. A significant exposure rate effect was also found, with low exposure rates more dangerous per unit of exposure than higher dose rates.
A method is developed based on earlier work by Prentice (1982) to adjust risk estimates for exposure measurement error. Contrary to a known downward bias in risk estimates due to non-differential misclassification, an upward bias in relative risk estimates is shown when using the log-linear risk function with certain distributional forms of covariate measurement error. A method for eliminating this bias is demonstrated.
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CHAPTER I

INTRODUCTION AND REVIEW OF THE LITERATURE

1.1 Introduction

The development of statistical methodology for application to failure time data has been expanding at a rapid pace. Much of the original effort in this regard was focused on the needs of actuarial science, clinical research and medical investigations. In recent years increased interest in the area of occupational health has further broadened the scope of application for survivorship models. It is the aim of this research to produce a quantitative risk assessment of lung cancer in U.S. uranium miners based upon available data concerning cumulative exposure. In order to achieve this goal we must identify an appropriate model and risk function, investigate the cancer mechanisms operating in this cohort and develop a method for addressing the errors in individual exposure estimates.

By their very nature occupational health studies are beset with a bewildering array of problems that range from selecting the appropriate group for study to drawing valid inferences from the results. We will limit the examination of these problems to those
encountered after the data have been collected. Some suggestions will be made, however, concerning ways in which the design and data collection protocols could have been improved. Obviously selection of statistical methodology for data analysis will be dictated by features of the data gathering process over which we had no control.

The next section will describe the particular cohort under study and the reasons for its choice. Because of past and present interest in this cohort, the literature review will necessarily include references to past work on this study of a general nature, as well as references concerning the particular statistical methodology appropriate to these types of studies.

1.2 Description of the Cohort

Beginning in 1950, the U.S. Public Health Service began medical examinations of uranium miners and mill workers in the states of Arizona, Colorado, New Mexico and Utah. Before 1954 this was done on a small scale with limited resources. During the period 1954-1960, however, an attempt was made to examine all known uranium miners in the four-state area. In 1957 and 1960 approximately 90 percent of the miners in these states were examined (Wagoner, 1964).

In order to form a study group (cohort) for later follow-up, certain criteria were defined. Individuals were included in the study if they had provided social and occupational data via a questionnaire interview and had volunteered for at least one physical examination. Lundin, et al (1971) estimated that approximately 90 percent of all
miners visited in 1957 and 1960 volunteered for the physical exam. They were also required to have been engaged in underground uranium mining for at least one month. This definition resulted in a cohort consisting of 3366 white and 780 non-white male underground uranium miners (Lundin, Wagoner, and Archer, 1971).

Follow-up began at the time of first examination (between 1950 and 1960) and is still on-going. Information on deceased miners was obtained from the Social Security Administration, the Internal Revenue Service, the Veteran's Administration and state vital statistics offices. Additional information on the living was obtained through an annual census by mail questionnaire. Due to this extensive follow-up procedure less than 1 percent of the cohort was lost to observation (Lundin, et al. 1971).

When follow-up indicated that a miner had died, a death certificate was obtained. The underlying cause of death was coded by a qualified nosologist according to the Seventh Revision of the International Classification of Diseases, adapted. The disease of interest in this study was lung cancer as defined by an ICD code of 162 or 163.

1.2.1 Description of Data

Detailed occupational histories were recorded by personal interview at the time of each examination and were supplemented through the annual census, work records (when available) and mail questionnaires. The number of separate work histories (mines) recorded on each individual in the cohort ranged from 1 to 23. These usually
consisted of work periods in different mines in the area. Personal data such as age, height and smoking habits were obtained at the same time.

The exposure of interest is radon daughters. Ores bearing uranium give off the inert gas radon which diffuses into the air throughout the mine. Radon decays (half life = 3.8 days) into radioisotopes of polonium, bismuth and lead. These "daughters" of radon attach themselves to airborne dust particles which are inhaled. Deposition of these particles in the lungs results in radiation exposure primarily to alpha particles (half life=30 minutes). The unit of measurement for radon daughters is a "Working Level" (WL) which is defined as any combination of radon daughters in one liter of air which results in the ultimate release of $1.3 \times 10^5$ MeV of potential alpha energy.

1.2.2 Estimation of Exposure

Between 1951 and 1968 almost 43,000 radon daughter measurements were made to characterize exposure levels for approximately 2500 mines in the four-state area. Standard sampling and counting techniques were used by all organizations (mainly the USPHS) recording measurements (Lundin, et.al. 1971). For mines in operation prior to 1951 estimates of WL levels were made based upon knowledge of ore bodies, ventilation practices, and emanation rates in each locality.
When one or more radon daughter measurements were available for a mine in any given year, they were averaged to provide a WL value for that mine and year. When no samples were available for a given mine and year, an interpolation procedure was employed. When measurements were separated by five or more years, the annual average was assigned backward and forward in time for two years. It was decided that this was the maximum period during which one could assume that conditions in a mine had remained constant. If annual averages in a mine were separated by one to four years, the measurements adjoining the gap were averaged and assigned to each of the intervening years. If none of these procedures was applicable, it was necessary to use the average WL value for other mines in that locality for each year in question. One desirable feature of this procedure was that more measurements were taken in the larger mines, thereby weighting the WL estimates toward those mines employing the largest number of miners.

Another important aspect of this dose estimation procedure concerned the sampling strategy of the mine inspectors. After 1960 most measurements were made for control purposes. Therefore, air samples were generally taken in areas of the mines thought to contain the highest levels of radiation. Consequently, the annual WL averages attributed to most mines were probably higher than those that would have resulted from a random sample of typical work areas. The upward direction of bias in dose estimation is thought to be consistent, and will be addressed again later in risk estimation.
1.3 Previous Analyses of the Data

1.3.1 The Original Mortality Study of U.S. Uranium Miners

Historically, the primary outcome of interest in the uranium miners cohort has been lung cancer mortality. Even before the discovery of the atomic bomb, bronchogenic cancer was attributed to high radiation levels found in underground mines (Hueper, 1942). The U.S. Public Health Service first documented an increased risk of respiratory cancer in U.S. uranium miners in 1961 (Archer, et al., 1962).

The analysis by Archer was done on a study group that consisted of approximately 80 percent of the present cohort. The method used in the analysis was the modified life table technique. The study group was divided into four sub-groups according to race and duration of exposure as of 1957 (less than 3.0 years or more than 3.0 years). Person-years of exposure were accumulated in five year age groups and multiplied by age-specific mortality rates for major causes in the four-state area. The expected deaths were compared with observed deaths presumably by chi-square tests, although the actual method is not stated.

Results indicated a statistically significant elevation in lung cancer mortality for white males exposed for three years or more. There was increased lung cancer mortality in those exposed under 3.0 years, but the difference was not statistically significant. As is
usually the case with life table analyses, no account was taken of actual radiation dose or of smoking status.

1.3.2 Subsequent Updates of Life Table Analyses

The next updated analysis of the U.S. uranium miners cohort was outlined by Wagoner in a JNCI paper (Wagoner, et.al., 1964). The method of analysis was the life table as outlined by Cutler and Ederer (1958). This analysis was slightly different than that used earlier, which was attributable to the Berkson and Gage approach (1950). The Berkson and Gage life table analysis required that any miner contributing information to the analysis had to survive a certain minimum number of years, i.e., the T-year survival rate. The method proposed by Cutler and Ederer (although used previously) allowed each miner to contribute information, even if it was only for a fraction of any given time interval. This is often referred to as the actuarial method.

The Wagoner analysis found an SMR of 357 for respiratory cancer (ICD=160-164, Sixth revision) among white uranium miners. Although no investigation of other risk factors was made in the life table itself (other than age and duration of employment), Wagoner and colleagues attempted to examine the potential bias of smoking, foreign birth, genetic differences, urbanization, volunteering, and accuracy of death certificates. They apparently recognized that SMR's between strata were not strictly comparable when age distributions were different, but they felt that there was a genuine
increase in risk with increasing duration of employment. They concluded that smoking patterns and genetic differences were similar among duration of employment strata and therefore could not account alone for differences in SMR's between strata. Foreign birth and urbanization were discounted due to their rarity in the cohort. The effect of volunteering for physical examination could have biased the SMR upward if those miners already suffering from respiratory problems had a greater willingness to enter the study. The authors concluded that this effect was negligible since the median time from first examination to diagnosis of respiratory cancer was five years. Inaccuracy in death certificates was apparently also not a problem. Twenty-nine per cent of all deaths were autopsied and all reported respiratory cancer deaths in this group were confirmed histologically.

One year later the data was updated and analyzed again in a slightly different manner (Wagoner, et.al., 1965). This time cumulative smoking histories and cumulative radiation dose were incorporated into the analysis. Smoking was measured in pack-months and radiation was accumulated from date of first employment as working-level months (WLM). Six strata were used for cumulative dose. Life tables were run both adjusted and unadjusted for cumulative smoking status. The smoking adjustment was accomplished by using age and smoking specific death rates for the four-state area. The source of these rates was not specifically stated, so their validity cannot be determined. The analysis, however, indicated a highly positive dose-response relationship both
unadjusted and adjusted for cumulative smoking. Latency and age at first exposure were mentioned as factors related to the dose-response relationship but they were not included in any of the analyses discussed in the paper.

Another update of the cohort followed the mortality experience until September, 1967. An analysis of these data by Lundin and colleagues (Lundin, et.al., 1969) found the highest risk yet for respiratory cancer (SMR=620). This analysis attempted to analyze the effects of smoking more thoroughly. Using a random sample of white U.S. males provided by the National Center for Health Statistics and standardized mortality ratios of respiratory cancer by smoking categories (Haenszel, et.al., 1962) observed and expected rates were compared for smoking and non-smoking miners. The authors concluded that there was a synergistic relationship between radon daughter exposure and cigarette smoking. This conclusion was based upon 60 observed respiratory deaths compared to 15.5 expected among smokers versus two observed and 0.5 expected among non-smokers. The interpretation of these figures on additive and multiplicative bases will be discussed later. Also discussed was the effect of prior hard-rock mining, especially among those miners in the lowest cumulative dose category. It was speculated that, although radiation exposure is low in other types of underground mines, there may have been a confounding effect in the low dose group due to exposure prior to uranium mining. This conjecture was principally warranted by the fact that a disproportionate number of respiratory deaths occurred among those miners previously employed in hard-rock mining.
In 1971, prompted by the suggestions and review of the Ad
Hoc Committee of the National Academy of Sciences - National
Research Council, the most comprehensive document to date was
published concerning lung cancer among U.S. uranium miners. A
monograph by Lundin, Wagoner and Archer (1971) was jointly sponsored
by the National Institute for Occupational Safety and Health
(NIOSH) and the National Institute of Environmental Health Sciences
(NIEHS). In addition to a further update of the mortality
experience of the cohort, extensive tables and graphs were produced
detailing other variables measured on the group over time. The
study group was corrected slightly and redefined to contain 3366
white uranium miners with more than one month of underground
experience. The monograph reported the first attempt to investigate
such important factors as latency, exposure rate, "effective" dose
and absolute versus relative risk. In order to make this feasible,
an exposure-time-response model was developed. Although still using
a life table approach, this model weighted exposure using a
log-normal distribution over time. Therefore, exposures occurring
near the assumed median latent period were weighted higher than
those occurring either earlier or much later. Median latent periods
of 5, 10 and 15 years were used to estimate the radiation dose that
was "effective" in actually causing respiratory cancer. Although,
conceptually this model is superior to those applied earlier to the
data, the actual procedures and calculations necessary for its use
were not clearly presented. Nevertheless, the authors reported that
a ten year latent period in association with the relative risk model
provided the best fit to the data. No significant relationship was reported between exposure rate and respiratory cancer rates when corrected for cumulative exposure. In discussing the fit of the model a statement is made that exposure appears to be more effective per WLM at lower cumulative exposure levels. This would imply a non-linear concave downward dose-response model. Using a median ten-year latent period and log-normal weighting of radiation dose over time, Lundin, et al. estimated that the actual effect of one WLM per year was a 12 percent increase in relative risk. Since this estimate would predict enormous relative risks for the average miner, doubt is cast on the validity of the model or calculations.

1.4 Evolution of Survival Analysis Methodology

1.4.1 Product-Limit Method

Kaplan and Meier (1958) proposed a modification of the usual life table approach to eliminate age grouped survival. Their approach, often called the product-limit method, examines survival status of the cohort at each distinct failure time, thereby avoiding an arbitrary division of the time scale. Censored observations tied with failure times (uncensored observations) are moved slightly ahead in time. Breslow and Crowley (1974) examined both the actuarial and product-limit methods under a random censorship model. They concluded that the actuarial method produces positively biased estimates of the conditional probability of survival, while
the product-limit estimator is asymptotically unbiased. They note, however, that if the number of intervals is greater than ten, the degree of bias in the actuarial estimate is not serious.

1.4.2 Parametric Models

Numerous parametric models have been proposed to describe survivorship both in human and other populations. The exponential distribution with density function,

\[ f(t) = \lambda e^{-\lambda t} \]

was originally used primarily to describe life testing of electronic parts with \( \lambda \) representing a positive failure rate parameter (Epstein and Sobel, 1953). Zelen (1966) used the exponential distribution to model carcinogenesis in both animals and humans. Since that time the exponential has probably become the most frequently used distribution in survival studies.

A generalization of the exponential distribution allowing the hazard to change over time is the Weibull distribution. In its most general form it has three parameters (all positive) with hazard function:

\[ \lambda(t) = \lambda_0 (t-\delta) \gamma - 1. \]

The location parameter, \( \delta \), is generally considered to be known, but Dubey (1967) developed a graphical estimator for it independent of \( \lambda \) and \( \gamma \). This parameter can be useful in estimating latency, especially in animal carcinogenesis studies (Hornung, 1980).
Other parametric forms have been proposed, but have received somewhat less attention than the exponential and Weibull. These include the log-normal, gamma, Gompertz and Rayleigh distributions (Kalbfleisch and Prentice, 1980). Gehan and Siddiqui (1973) proposed a method for determining the best fitting model from among the exponential, linear hazard, Gompertz and Weibull distributions based on the likelihood of the four models. This method, however, has received little attention in practical applications reported in the literature.

1.4.3 Regression Models

The primary way of controlling the effects of extraneous risk factors in life table analysis is stratification. When the number of combinations of levels of such factors begins to get large, the cell sizes limit the usefulness of this technique.

Feigl and Zelen (1965) proposed a model for the estimation of survival probabilities in the presence of concomitant information. Their model assumed an exponential distribution of survival time, $t > 0$, such that the probability density function $f_i(t)$ for the $i$th person took the form:

$$f_i(t) = \lambda_i \exp(\lambda_i t)$$

and

$$E(t_i) = \frac{1}{\lambda_i} = a + bx_i,$$
where $x_i$ is the covariable for the $i$th person. Not only did this model provide a better way of handling continuous covariables, it also permitted the estimation of the functional form of the survival probability. The survival function for the $i$th patient $S_i(t)$ can be written:

$$S_i(t)=P(T_i>t)=\int_t^\infty f_i(u)\,du$$

$$=\exp(-\lambda_i t)\exp[-t(a+bx_i)^{-1}].$$

A drawback to this approach is the sometimes unrealistic assumption that the expected survival time $t_i$ is a linear function of the covariable $x$. In addition, the parameters $a$ and $b$ must be restricted such that $a+bx>0$ for any $x$ considered. Recognizing this, Feigl and Zelen proposed two additional functional relationships:

$$E(t_i)=(a+bx_i)^{-1},$$

or

$$E(t_i)=a\exp(bx_i),$$

where $a>0$. Of course, one still has to assume that the parent distribution of survival times is exponential.

The method proposed by Feigl and Zelen was not originally designed to include censored data. Zippin and Armitage (1966) extended the work of Feigl and Zelen to include situations when survival times were incomplete for some members of the study. They also considered the effect on asymptotic standard errors of the parameter estimates of simultaneous entry into the cohort versus entry at regular time intervals. It was shown that simultaneous entry reduced the size of the standard errors.
Glasser (1967) proposed a similar regression approach but one in which the hazard function was log-linear, taking the form:

$$\lambda_{ij} = \lambda_j \exp(bx_{ij})$$

for the $i$th individual in the $j$th group with covariate value $x_{ij} = x_{ij} - X$. In this model $\lambda_j$ is considered to be the true hazard in group $j$ for those individual with the mean value of the covariate. In this way Glasser extended the work of Feigl and Zelen to allow the hazard to change from group to group by having multiple intercepts with common slope. Likelihood equations were derived for estimation of the parameters.

Perhaps the most popular regression method for use in mortality studies is the logistic model. Originally proposed by Cornfield (1962) for use with such data, the logistic risk function models the relationship between the probability of death and various risk factors used as covariates in the model. Given a vector of covariates $z_i = (z_{i1}, z_{i2}, ..., z_{ik})$ for the $i$th individual, the model takes the form:

$$P(\text{ith individual dies during follow-up } z_i) = \frac{1}{1+\exp(-\alpha - \beta z_i)}$$

where $\alpha$ and $\beta$ are parameters to be estimated. Truett, et al. (1967) used this model to analyze data from the Framingham Heart Study and it has been used extensively since then. Originally linear discriminant analysis was used to estimate the parameters. However, after it was shown that bias would result if $z$ was not multivariate normal, maximum likelihood techniques were adopted. Proper use of
this model produces the popular odds ratio estimate of risk for a dichotomous risk factor:

\[ \text{OR} = e^\beta. \]

For continuous covariates

\[ \text{OR} = e^{\beta (z_1 - z_0)} \]

produces an estimate of the risk for an individual with covariate value \( z_1 \), relative to an individual with covariate value \( z_0 \). A negative aspect of this model is that it ignores the time at which each individual dies. Until recently the effect of this on risk estimation was not fully appreciated. Such factors as latency, length of follow-up and rarity of disease can all affect risk estimates produced by logistic regression. Breslow and Day (1980) recommend dividing the data into time strata if follow-up is long. Green and Symons (1983) show that the logistic model yields good approximations to results from the proportional hazards model only when follow-up is short and the disease is rare. An additional requirement is that follow-up times for individuals in a study group must be similar in order for logistic regression to be appropriate. This is related to the problem of dealing with censored data. In general, logistic regression does not consider censoring patterns unless the analysis is conditioned upon individuals at risk at each failure time, i.e., conditional logistic regression.
1.4.4 The Cox Model with Fixed Covariates

Cox (1972) generalized the work of Feigl and Zelen, Zippin and Armitage and others by suggesting that the hazard rate should be allowed to change with time and, in a unique proposal, assumed that the underlying hazard, $\lambda_0(t)$, was arbitrary. His hazard function takes the form:

$$\lambda(t;z) = \lambda_0(t) \exp(\beta z).$$

Cox argued that since nothing is known about $\beta$ in the interval between failures, the model should be conditional upon the exact observed failure times. That is, for any particular failure time $t_i$, the probability that an individual with covariate vector $z_i$ dies at time $t_i$ is conditional on those surviving to $t_i$ (the risk set $R(t_i)$) and, assuming no ties in failure time, is equal to:

$$\exp(\beta z_i) / \sum_{j \in R(t_i)} \exp(\beta z_j).$$

Since each failure contributes one such factor the "conditional" likelihood is the product of factors such that

$$L(\beta) = \prod_{i=1}^{k} \frac{\exp(\beta z_i)}{\sum_{j \in R(t_i)} \exp(\beta z_j)}.$$ 

By inspecting the likelihood equation an interesting point becomes evident. The likelihood equation, and therefore the estimate of $\beta$
are independent of the exact failure times. That is, a simple rank ordering of the failure times will result in the same estimate of \( \beta \) as the original vector of failure times \( t_1, \ldots, t_n \).

Although Cox originally referred to the "conditional" likelihood, it was pointed out by Kalbfleisch and Prentice (1972 and 1973) and later by Cox himself (1975) that this was not strictly true. In their 1973 paper Kalbfleisch and Prentice show that the original Cox likelihood is actually a marginal likelihood when there are no ties among failure times and \( z \) is not time-dependent. However, in the case of tied death times their marginal likelihood is different from that of Cox. Breslow (1974) suggested a computationally simpler likelihood which yields a good approximation to the discrete likelihood of Kalbfleisch and Prentice when the data are not heavily tied:

\[
L(\beta) = \prod_{i=1}^{k} \left( \frac{\exp(\beta s_i)}{\sum_{j \in R(t_i)} \exp(\beta z_j)} \right)^{m_i}
\]

where \( s_i \) is the sum of \( z_j \) over the \( m_i \) individuals failing at \( t_i \). Cox conceded in his 1975 paper that his original equation was not a true conditional likelihood but that it was a partial likelihood still suitable for inference concerning \( \beta \).
1.4.5 Time-dependent Cox Model

One of the most important aspects of Cox's model was the option to use covariates which change over time. Originally Cox conceived the idea of defining a time dependent covariable as the product of a fixed covariable and time \( t \) itself. This provided a simple way of testing the proportional hazards assumption, i.e., the assumption that hazard ratios remain constant over time. A more valuable application, however, is the incorporation of prognostic factors into the model which themselves are functions of time. An important example of such a time-dependent variable is cumulative exposure as often defined in occupational health studies.

The partial likelihood expression looks essentially identical to the one used for fixed covariates with no ties in failure times:

\[
L(\beta) = \prod_{i=1}^{k} \frac{\exp(\beta z_i(t_i))}{\sum_{j \in R(t_i)} \exp(\beta z_j(t_i))}
\]

where \( z(t_i) \) is the covariate vector evaluated at time \( t \).

Computationally, however, there can be a vast difference between a model with fixed covariable and one with time-dependent covariables. This results from the fact that the contribution to the likelihood at each failure time \( t_i \) may involve an entirely new set of covariables for each person remaining in the risk set. This problem will be discussed in more detail in Chapter II.
Conceptually, this approach is similar to that proposed by Mantel (1966) and applied to heart-transplant data by Mantel and Byar (1974). This approach considers several categorical states (e.g. treatment groups) which contain individuals at risk at each failure time, \( t_i \). In the simplest case of two groups a 2 x 2 contingency table of the form

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is formed at each failure time with censored observations assumed to occur at the end of the interval. The time-dependent nature of this model stems from the allowance of individuals to move from one treatment to another over time. Therefore, \( N_{1i} \) and \( N_{2i} \) do not necessarily decrease from one failure to the next.

1.5. Variations of the Cox Model

The introduction of the Cox model in 1972 immediately inspired widespread interest in various derivations based on his original proposal. In commenting on Cox's paper, Breslow (1972)
suggested that $\lambda_0(t)$, rather than purely arbitrary, could be considered constant between failure times so that

$$\lambda_0(t) = \lambda_1, \text{ for } t_{i-1} < t \leq t_i.$$  

Cox responded that this proposal resulted in the intervals contributing no information concerning $\beta$ and introduced a dangerously large number of nuisance parameters into the likelihood equations without substantial improvement in his approach. Holford (1976) proposed a model similar to Breslow's but with the hazard $\lambda_0(t)$ constant in any of $k$ time intervals chosen by the investigator.

Kalbfleisch and Prentice (1973) proposed a grouped data version of the proportional hazards model with many tied failure times. Prentice and Gloeckler (1978) extended this generalization to include time dependent covariates, although forcing them to be constant within each interval.

The original Cox model without time-dependent covariates requires the assumption that the ratio of hazards for any two values of $z$ remain constant over the entire period of study. Kalbfleisch (1974) generalized the proportional hazards assumption by introducing stratification into the model which only required proportionality within strata. This development allowed the analyst to remove from $z$ those covariates not following the proportional hazards assumption and then introduce them as stratification variables. The hazard for a person in the $j$th strata is then:

$$\lambda_j(t; z) = \lambda_{0j}(t) \exp(\beta z).$$
The underlying hazard, therefore, varies over the strata but the vector of regression coefficients \( \beta \) remains constant.

In a similar development Holt (1978) proposed a variation of the Cox model to handle competing risks. He considered two different models:

Model 1: \[ \lambda_1(t, z, j) = \lambda_0(t) \exp(\beta_j z) \]

Model 2: \[ \lambda_2(t, z, j) = \lambda_0(t) \exp(\beta_j z). \]

Model 1 maintained the proportional hazards assumption but allowed the coefficients to change for cause \( j = 1, \ldots, k \). Model 2 was more general and permitted the shape of the hazard and the coefficients to all change over the causes of interest. Prentice et al. (1978) extend this model to time-dependent covariates and discuss the effect of removal of some causes on the failure times for others.

Due to computational difficulties typically encountered when using the full time-dependent Cox model, a sample based case-control approach was developed by Liddell, McDonald and Thomas (1977) and expanded upon by Prentice and Breslow (1978). Their idea was to select a sample of controls from the current risk set at each case's failure time. It was shown that this reduced to a logistic model conditional on the sampled risk set with the same likelihood function as Cox's original approach. That is, the conditional likelihood

\[
L(\beta) = \prod_{i=1}^{k} \left[ \frac{\exp(\beta z_{i0})}{\sum_{j \in R_i} \exp(\beta z_{ij})} \right]
\]
is the product of \( k \) terms (one for each distinct failure) representing the conditional probabilities that vector \( Z_{i0} \) corresponds to the only case out of the total sampled risk set \( R_i \) at failure time \( t_i \). If \( m_i \) failures occurred at any time \( t_i \) the contributions to the likelihood were of the form:

\[
\exp(b_{s_i}) / \sum_{j \in R(m_i)} \exp(b_{s_j})
\]

where \( s_i \) is the sum of the \( z_i \) for the \( m_i \) cases and \( s_j \) is the sum of the \( z_i \) for the \( j \)th subset of size \( m_i \) out of a total of \( \binom{R_i}{m_i} \) possible subsets.

Prentice and Breslow (1978), Kleinbaum, Kupper and Morgenstern (1982) and others have indicated that when \( R_i \) and \( m_i \) are large the conditional logistic model is not feasible. In those situations the usual unconditional logistic model provides a viable alternative. However, Breslow and Day (1980) show that when stratum sizes (matched sets) are small as in \( R:1 \) matching schemes with \( R \leq 4 \), severe bias may result when using the unconditional model. In fact, in pair matched designs they showed that the unconditional model will overestimate the odds ratios by the square of the true value. Therefore, in the commonly used \( R:1 \) matched designs with \( R \leq 10 \), the conditional logistic model is the method of choice.

Breslow and Patton (1979) considered the efficiency of designs where each failure was matched to \( R \) controls sampled from the risk set at the time of failure. Their work was an extension of asymptotic efficiency estimates for matched case-control studies provided by
Ury (1975). They concluded that the efficiency of such a design compared to one where an arbitrarily large number of controls were used was \( R/R+1 \). Thus the use of more than four controls per case meets with diminishing returns. Whittemore and McMillan (1982) point out that this is only true for a single dichotomous exposure variable and a true relative risk near 1.0. Breslow et al. (1983) conclude that substantially more than four controls per case should be sampled if the true relative risk is likely to be high, exposure is rare, and the primary interest is precise estimation of relative risk (as opposed to hypothesis testing).

Because of the arbitrary nature of the underlying hazard, \( \lambda_0(t) \), only internal comparisons are possible when using the Cox model. Breslow (1977) proposed a modification to the Cox model which replaced the unknown function \( \lambda_0(t) \) with annual cause specific death rates for some appropriate demographic comparison group, e.g., U.S. rates. Gilbert (1983) applied both methods (internal and external comparisons) to the Hanford worker's radiation exposure data. Based on power calculations she concluded that the use of external rates is slightly better if they are indeed the correct underlying rates, and the cause of death is rare. However, when the healthy worker effect (Enterline (1975) and McMichael et al. (1975)) is present and the cause is not rare, the reverse may be true.

Another solution to the specification problem for the underlying hazard was proposed by Taulbee (1979). He allows the hazard to be a polynomial in time with the coefficients being different functions of the vector of covariates. This allows the hazard ratio
for individuals with different covariate vectors to change over time. This approach has the additional advantage of being "nearly non-parametric" in that a polynomial can approximate the shape of any reasonable hazard function.

1.6 Applications of the Cox Model

Breslow (1974) applied three models all of the form

\[ \lambda(t, z) = \lambda_0(t) h(z, z) \]

to a clinical trial of maintenance therapy for childhood leukemia. Models I and II both assumed \( \lambda_0(t) = \lambda \) for all \( t \), with

Model I: \[ \lambda(t, z) = \lambda(1 + a z)^{-1} \]

and

Model II: \[ \lambda(t, z) = \lambda \exp(\theta z). \]

Model III was the modification of Cox's model described earlier where the underlying hazard was constrained to be a non-zero constant between each failure time. Time was measured from entry in the trial to relapse and the covariate vector \( z \) consisted of indicator variables for treatment regimen as well as baseline covariates of WBC and age at entry. Results indicated that parameter estimates were similar for Models II and III but both different from Model I. Breslow concluded that the modified Cox model justified the additional computational price with greater robustness and additional power. Caution was urged in assuming parallelism for baseline covariates across treatment groups in similarly designed studies.
Gilbert (1979) applied a modification of the Cox model to data from Hanford workers exposed to radiation. She replaced the multiplicative factor $\exp(\beta z)$ with $1 + \beta z$ and tested the hypothesis $H_0: \beta = \beta_0$ where $\beta_0$ was a large effect. The extremely skewed nature of exposure data presented problems. A square root or log transformation was suggested since measurement error likely increased with higher dose. Gilbert noted that a lagged measure of dose still showing a dose response was necessary for credibility in cancer mortality studies.

Liddell et al (1977) applied three methods to data from workers involved in mining and milling of asbestos. They compared and contrasted the results of a traditional SMR approach, the Cox regression model, and a matched case-control method. Although the three methods produced similar results, they preferred the a posteriori case-control approach because of its simplicity of use and interpretation. In using the Cox model age was treated as the time dimension and covariates of interest were entered in a stepwise fashion. The authors noted that, while this model facilitates the study of interactions, it was by far the most expensive computationally.

Crowley and Hu (1977) used the Cox model to assess the effects of various covariates on the survival of patients in the Stanford Heart Transplantation Program. They were among the first to use time-dependent covariates in this model. These covariates, however, were treated as step functions, assuming a value of zero
until transplant date and their actual value afterwards. In fact, the time-dependent covariate "transplant status" being dichotomous cannot be evaluated statistically, but in essence serves as an intercept in the presence of other time-dependent covariates. This paper also attempts to examine goodness-of-fit by stratification and examination of residuals in models without time-dependent covariates.

Kneale, Mancuso and Stewart (1979) applied the proportional hazards model to radiation-exposed Hanford workers without the use of time-dependent covariates. Of interest among their findings were a concave downward dose-response curve and a latency period of 25 years for cancers of radio-sensitive tissues. Because dose data from this study consisted of annual radiation exposure in rads measured by film badges, it is ideal for study of both cumulative dose and dose-rate effects. The authors note, however, that dose rate was nearly constant over time and thus radiation dose and duration of employment are highly correlated. Therefore, investigation of dose rate was not feasible.

Farewell (1979) investigated the usefulness of time-dependent covariates in a prospective study of infection in anaemia and leukemia patients after bone marrow transplants. A variety of covariates were examined, both fixed and time-dependent. Of particular interest was the author's interpretation of the marginally significant covariate corresponding to granulocyte level in a stratified model. Farewell felt that a stronger relationship between this time-dependent covariate and infection actually existed
but was not detected due to the arbitrary nature of the underlying hazard, $\lambda_0(t)$. As Efron (1977) showed in his paper on the efficiency of Cox estimates, the amount of information contained in the coefficient of a time-dependent covariate depends upon the conditional variance of the covariate in each risk set evaluated at each failure time. In essence, a time-dependent covariate varies in two dimensions - across time and across members of the risk set. If a covariate changes markedly over time but in such a way that its variation within risk sets is minimal, little information concerning its effect on survival will be gained. This problem is even more striking if stratification variables are employed that cause members of each strata to be homogenous with respect to the time-dependent covariable. The Cox model will simply interpret any change in death rates actually due to the covariate as a change in the underlying hazard which is allowed to vary from stratum to stratum. This phenomenon is especially important in occupational studies where one may wish to model cumulative dose as a time-dependent covariate when it is positively correlated with such variables as age and duration of employment.

1.7 Outline of Subsequent Chapters

In Chapter II, a protocol for mortality analysis of the U.S. uranium miners cohort is outlined. The original Cox model is generalized to include different forms of the hazard function. Time-dependent covariables describing cumulative radiation dose,
dose rate and smoking history are introduced and methods for assessing goodness-of-fit are outlined. Possible measures of 'effective dose' are proposed. Software is developed and described which enables the data analyst to manipulate risk sets, which is often necessary when age is the time dimension, and to introduce alternative forms for the hazard function. Stages in developing the final model are reported and discussed. Chapter III investigates the possible cancer mechanisms operative in the cohort. Assuming some form of the multi-stage model postulated by Armitage and Doll (1961) inferences are drawn concerning the stages of carcinogenesis affected by exposure to radon daughters and cigarette smoking. Temporal variables examined in this analysis include age at first exposure, time since last exposure, latency distribution, and duration and/or level of exposure.

Chapter IV builds upon the results of the previous two chapters, to produce a quantitative risk estimate for lung cancer particularly in the area of 120 WLM of cumulative exposure. This risk assessment introduces a statistical method for dealing with errors in measurement of exposure.

In Chapter V suggestions are made for further research concerning the subject matter or related topics.
CHAPTER II
Application of the Time-dependent Cox Model to
U.S. Uranium Miners Data

2.1 Introduction

The aim of this chapter is to select and apply a statistical
model to data available on members of the cohort of U.S. uranium
miners. Extensive information is available on 3,347 white male miners
which is conducive to the use of a regression technique such as the
time-dependent Cox model. The objective of this analysis is the
creation of a concise, credible model for use in Chapters III and IV in
the quantitative assessment of risk of lung cancer after exposure to
varying levels of radon daughters.

Development of the model involves several distinct
considerations. Potential confounders and effect modifiers will be
investigated using likelihood ratio tests. Alternative forms of the
dose-response function are considered. The relationship between
cigarette smoking and exposure to radon daughters will be explored to
determine whether it is super- multiplicative, multiplicative or
submultiplicative. Finally, goodness-of-fit of the model will be
tested using a "saturated" model involving cross-products of levels of
the selected risk factors.
2.2 The Time-dependent Cox Model

The model chosen for initial application to the uranium miners data is the proportional hazards model:

$$\lambda(t; z(t)) = \lambda_0(t) \exp(\beta z(t)).$$

The Cox model produces incidence rate ratios as opposed to approaches such as the logistic model, which deals with risk ratios. The principle difference is that rate ratio models incorporate incidence of events over the period of study, whereas models for risk usually compare the cumulative effects at the termination of the study. If follow-up times are relatively short and similar among comparison groups, both approaches should yield similar results. However, if follow-up is lengthy and varies among comparison groups (as is the case with the U.S. uranium miners), a method incorporating incidence rates over time would be preferable. Good discussions of this issue are found in Kleinbaum, Kupper and Morgenstern (1982), Greenland and Thomas (1982) and Green and Symons (1983). In the remainder of this study we shall refer to the ratio of hazard rates as relative risks, although strictly speaking they are rate ratios.

An additional advantage of the Cox model is that it can incorporate covariates that change over the period of study. When this time-dependent version of the model is employed, the computational time dramatically increases. This is due to the fact that all time-dependent covariates must be re-computed at each failure time in order that the proper contribution to the likelihood equations is
made. That is, the contribution to the overall likelihood at the ith failure time is the ratio:

$$\exp(\beta z(t_i)) / \sum_{j \in R(t_i)} \exp(\beta z_j(t_i))$$

where all covariates assume values appropriate at time $t_i$.

The statistical software used to implement the time-dependent Cox model was the BMDP2L procedure with recent modifications to accommodate time-dependent risk sets and general risk functions (see BMDP Technical Report No. 80, Hopkins and Hornung, 1985). An example of a typical time-dependent computer run using this procedure is provided in Appendix A. Modifications to the existing procedure were required since time ($t$ in $\lambda(t; z)$) in the model was taken to be age at death or end of follow-up. This was originally suggested by Liddell, McDonald and Thomas (1977) and later by Breslow, et al. (1983). The reasoning for this approach is two-fold. First age is so strongly related to cancer incidence that it is important to control it as closely as possible, which may be difficult using covariate adjustment or stratification. Second, the alternative of using the survival period as the time dimension may partially mask the effect of radiation exposure since survival time and cumulative exposure are highly correlated. In effect, the use of age as the time dimension "matches" each failure to the members of his comparison group (risk set) on age. By then stratifying on year of birth the model provides a useful way of handling the two time dimensions affecting most cohorts - age and calendar year.
2.2.1 Computational Issues

While use of age as the time dimension is often a desirable approach, it presents a problem to some software routines used for Cox models. Since members of most cohorts enter the study at varying ages, the size of the risk sets does not monotonically decrease as the failure times increase, as is the case when using survival time since entry into the study. Therefore it is necessary to control membership in the risk set for each failure time. That is, a person is removed from consideration in the likelihood equations if he had not yet entered the cohort at the age of the failure being considered.

The necessity for control of membership in the risk set at any given failure time required modification of the BMDP program used in the analysis. The author, Alan Hopkins, was contacted and agreed that these changes were necessary for a flexible analysis routine. The modifications made to the BMDP2L procedure include control of membership in each risk set, optional user-supplied alternatives to the usual log-linear risk function, and optional use of conditional logistic regression for matched case-control studies.

As mentioned earlier, the computational time required for use of the time-dependent Cox model with the full cohort is considerable (150-300 CPU seconds using an IBM 3380 main frame). There are essentially two ways to reduce the CPU time: stratification or sampling each risk set. Stratification may substantially reduce the computational time since the size of the risk set associated with each failure is reduced and therefore fewer calculations are made in
re-evaluating time-dependent covariates at each failure time. Sampling each risk set by randomly selecting 10-20 "controls" at each failure time produces the most efficient design in terms of computer time used. This technique produces coefficient estimates that are very close to those using the full cohort while the standard errors are slightly larger. (Breslow, et al. 1983 and Steenland, Beaumont and Hornung, 1985). Because CPU time was not an essential consideration in our analysis, we decided to use the full cohort stratified by birth year in ten year intervals. For most other situations, however, the method of choice would seem to involve sampling the risk set unless either the cohort was small or very precise estimates were desired.

2.2.2 Description of Data Used in the Model

The work history for each miner was used to create a cumulative dose profile. The times (ages) at which each miner accumulated certain pre-specified benchmark exposure levels of radon daughters were available for use in estimating the cumulative exposure at each failure time. In a similar manner, smoking histories were available to document the times at which a miner changed smoking rates. These data were used in a FORTRAN subroutine to estimate by linear interpolation each miner's cumulative exposure (WLM), exposure rate (WLM/month), cumulative cigarette smoking (packs), and smoking rate (packs/day) at any given time.

Other variables considered in the model are listed in Table 2.1. Height may seem to be a questionable choice for a
possible relationship with lung cancer, but this covariate was included because Archer, et al. (1978) reported this to be a significant risk factor. They reported increased risk for miners less than 68 inches in height. They interpreted this result by hypothesizing that smaller miners may have to work harder than their larger co-workers and therefore inhale more radon daughters per hour of work.

Duration of employment (TOTMON) was a cumulative total of working months in underground uranium mines. All gaps in underground work histories were omitted since mining is a very cyclical form of employment.

2.3 Statistical Protocol for Analysis

2.3.1 Preliminary Investigation of the Data

Before fitting various models to the data, a preliminary look at the lung cancer mortality experience of the cohort and the distribution of potential risk factors was desired. As shown in Table 2.2, a little less than 30 percent of the cohort was deceased as of the end of 1977. However, almost 20 percent of total deaths were due to lung cancer. Even though these are crude totals, it is obvious that there is elevated risk of lung cancer in this cohort, since the lifetime risk of lung cancer in males is approximately 6 percent. This research is not intended to verify what many others have established in earlier work, but to quantify risk from radon daughter exposure in the presence of potential confounders and/or effect modifiers.
The discrepancy between the 3,347 white miners reported in this study versus the 3,366 reported in the 1971 monograph is due to several apparent misclassifications. Four miners originally included were determined to be non-white, and 10 miners were eliminated because they never worked underground. The remaining five miners had missing or insufficient smoking information.

Inspection of Table 2.1 indicates that uranium miners were heavier smokers than the average population (only 20 percent never smoked). They began underground mining at a somewhat later age (median age = 29 years) and worked a shorter period of time (median duration = 48 months) than most occupations. All continuous variables show a wide range of values with a distribution skewed to the right. Covariates assuming such wide ranges have potentially strong effects on any regression model, and therefore each variable must be carefully considered.

2.3.2 Outline of the Model

As mentioned in section 2.2 the time-dependent Cox regression model will be the basic analytical tool used to assess lung cancer risk in this cohort. Specifically, the stratified version of this model:

$$\lambda_j(t;z) = \lambda_{0j}(t) \exp(\beta z)$$

is the method of choice. The underlying or baseline hazard is allowed to change with strata $j$, while the coefficients of each covariable remain constant across strata. The stratification variable is birth
year divided into four intervals: before 1901, 1901-1910, 1911-1920, and after 1920. Since the time dimension used in the models is age, this stratification ensures that all miners in a given risk set are evaluated at the same age and were born within 10 calendar years of one another. This approach should remove any age or cohort effects from the analysis.

Initial attempts at fitting models involved lagging exposure and smoking eight years. This was done because of two different reasons: exposure and smoking information was last updated in 1969 while follow-up ended in 1977, and lung cancer is known to have a relatively long latency period. A more detailed investigation of the appropriate lag period or a similar time-weighting scheme will be undertaken in Chapter III.

The primary objective of model development is the determination of the functional form of the relationship between radon daughter exposure and the lung cancer mortality rate. This is possible only by considering the effect of potential confounders and effect modifiers. The candidates for confounders or effect modifiers are cigarette smoking, age at initial exposure, calendar year of initial exposure, prior hardrock mining experience, height and birth year. In attempting to determine the most appropriate exposure index, the exposure rate, as well as cumulative exposure, were also added to the list of covariables.
2.4 Model Development

2.4.1 Initial Model

The first model successfully run is given in Table 2.3. Initially an attempt was made to fit a model with all main effects and two-way interactions involving cumulative exposure. The Newton-Raphson algorithm for maximum likelihood estimation did not converge for this model. This was probably due to a near-singularity in the design matrix for this large model (17 terms) (Mason et al. 1975).

Inspection of Table 2.3 indicates that neither the average exposure rate nor the rate of cigarette smoking were useful in explaining the relative risk of lung cancer when cumulative exposure and cumulative packs of cigarettes were in the same model. This result agrees with previous work by Lundin, et al. (1971) and Whittemore and McMillan (1983), since neither study of this cohort was able to find an exposure rate effect in the presence of cumulative exposure using the life-table and matched case-control approaches, respectively.

The covariables corresponding to prior hardrock mining, smoking rate and exposure rate were removed, and the model refit. The likelihood ratio test for the combined contribution of these three variables can be computed by taking twice the difference in log-likelihoods for the respective models. This statistic is approximately chi-square with three degrees of freedom. The results of this test were chi-square=0.64, p=0.89. This lack of statistical significance and the fact that the coefficient for cumulative exposure changed very little, suggest that removing these three variables was well justified.
2.4.2 Assessment of Confounding Effects

In order for a variable to be a confounder it must be both a risk factor for the disease of interest and also have an effect upon estimation of the risk associated with exposure. In developing the model, it became apparent that elimination of various non-significant variables had little effect upon the relative risk estimate for cumulative exposure. These variables therefore were eliminated as candidates for confounding effects.

The one most important risk factor to be considered in any study of lung cancer etiology is cigarette smoking. In this cohort cumulative smoking, as measured by total packs smoked, is strongly related to the risk of death from respiratory cancer. This is especially important in this cohort since approximately 80 percent of all members were current or ex-smokers.

In order to assess the confounding effect of cigarette smoking on the relationship between lung cancer risk and radon exposure, models were fit with radon exposure alone and then with cigarette smoking added to the model. Results indicated that smoking had little if any confounding effect upon the risk associated with cumulative radon exposure, i.e., the change in the coefficient for cumulative exposure was negligible after adding smoking to the model (0.319 vs 0.325). Since no interaction with smoking was found, smoking apparently has a strong independent multiplicative effect on the risk of lung cancer for uranium miners. This implies that the risk for highly exposed miners relative to low exposed miners with the same smoking history does not
depend upon the level of smoking. However, the risk for a smoking, highly exposed miner relative to a non-smoking, low exposed miner is the product of individual risks associated with radon exposure and smoking.

In most occupational studies of lung cancer risk, cigarette smoking overshadows the occupational carcinogen in terms of relative effect. However, radon daughter exposure among uranium miners is one of the few carcinogens that supercedes the strong effect of smoking. In terms of relative potency, the Cox model predicts that a miner would have to smoke over 37,000 packs or 103 pack-years of cigarettes to equal the relative risk of lung cancer for a miner with the median exposure of 430 WLM.

2.4.3 Assessment of Effect Modification

After dropping the three covariates mentioned above, a new model was fitted which consisted of the five main effects and the four two-way interactions involving cumulative exposure. The results are given in Table 2.4. The likelihood ratio test for all four two-way interactions produced chi-square = 6.48, P = 0.17. Clearly, addition of these terms adds little to the fit of the model. In fact, the introduction of the four interactions seemed to produce a somewhat unstable model as evidenced by the dramatic increase in the standard error for cumulative exposure. Because the effect of cigarette smoking is of special interest in any lung cancer study, its interaction with radon exposure was assessed again in the absence of additional
interaction terms. As before, the coefficient for this interaction was not significant (β=-0.003, p=0.62).

The model was reduced to one containing three terms: cumulative exposure, cigarette packs, and age at first exposure. This model was apparently more stable in that the standard errors were in general much smaller, especially for cumulative exposure. All three were highly significant.

In order to check for homogeneity of the relative risk estimates across birth year strata, the interaction between cumulative exposure and birth year was added to the above three variable model. Results showed that this interaction was significant (chi-square = 11.7, p<0.001). The coefficient (β=0.012) was positive indicating that miners born in later decades were at increased risk per unit of exposure relative to miners born earlier.

2.5. Estimation of the Functional Form of Dose-Response

Having determined that the terms for cumulative exposure and cumulative smoking are important risk factors, various forms of the dose-response relationship within the proportional hazards framework were investigated. With that goal in mind, quadratic terms for each factor were added to the model. The results were striking as can be seen by examination of Table 2.5a. The likelihood ratio test for inclusion of the two quadratic terms produced chi-square = -2(1025.7-1059.8)=68.2 with two degrees of freedom. The coefficients were both highly significant and negative. This indicates that the
relative risk function for both radon daughter exposure and cigarette smoking is concave downward. However, such quadratic dose response functions also predict a maximum response at approximately 10,000 WLM and then a decrease in risk subsequently. Therefore, other convex functions were investigated which may be more biologically plausible.

Since both cumulative exposure and cumulative smoking levels were highly skewed, a reasonable transformation which may take the shape of a concave downward curve is the natural logarithm. In order to avoid zero levels for either exposure or smoking, background levels of each were added to the data. Estimation of these levels from the data would be difficult and would likely increase standard errors of other coefficients in the model. Therefore, external estimates of background exposure to radon daughters and cigarette smoking were used. Papers by Hanchey (1981) and George and Breslin (1978) estimate that approximately 0.2 WLM per year is a reasonable background radon level. Therefore, this annual increment was added to each miner’s cumulative total. Similarly, 0.005 packs per day, as estimated by Hinds and First (1975), were added to every miner’s cumulative smoking totals. A three parameter model involving log exposure, log smoking and age at initial exposure was then fit. (Table 2.5b) This model involving two less parameters than the quadratic model in Table 2.5a had essentially the same log likelihood.

In order to investigate the sensitivity of the model to changes in background estimates, various other background rates were tried, ranging from 0.1 WLM/year to 0.4 WLM/year for radon daughters and 0.002 packs/day to 0.01 packs/day for cigarette smoking. These
analyses indicated that small changes in background had little effect upon the coefficient estimates or the log-likelihoods for the model. In addition to the simplicity of the log-transformed model another attraction is its ease of interpretation. Since the risk function is of the form \( \exp(\beta z) \) substituting \( \ln(z) \) for \( z \) produces a simple power function: \( \exp(\beta \ln(z)) = \prod_i z_i^\beta_i \). Since the coefficients of both smoking and exposure are less than 1.0, each of their dose-response functions are concave downward as was the case for the quadratic model. A plot of relative risk as a function of radon daughter exposure is given in Figure 2.1. Confidence limits were calculated as 1.96 multiplied by the standard error of the coefficient. The coefficient for cumulative exposure (\( \beta_1 = 0.635, \text{std. error}=0.067 \)) and the coefficient for cumulative smoking (\( \beta_2 = 0.389, \text{std. error}=0.068 \)) indicate that the relative risk for lung cancer varies with roughly the square root of both cumulative exposure and cumulative smoking.

These results are similar to those of Whittemore and McMillan (1983) in a case-control analysis of the U.S. uranium miners data. They also found the log transform to provide a better fit, although their coefficients were somewhat different: \( \beta_1 = 0.434 \) (std. error=0.058) for exposure and \( \beta_2 = 0.411 \) (std. error=0.072) for smoking. The lower value for the coefficient of cumulative exposure is probably due to two reasons. First, they used a 10 year lag which reduces the coefficient compared to the eight years lag used here. This will be explored thoroughly in Chapter III. Secondly, they only matched four controls to each case. Breslow, et al. (1983) among
others, show that as many as 10 to 20 controls per case may be necessary when the overall relative risk of interest is much greater than 1.0. In addition, Whittemore and McMillan also did not find age at start of underground mining to be a significant risk factor, once again possibly due to the matching scheme.

2.6 Goodness-of-fit for Dose-response Model

The overwhelming statistical significance of the stratified dose-response model (i.e., under $H_0: \beta = 0$) involving log exposure, log smoking and age at initial exposure (chi-square = 171.4, d.f. = 3) inspires confidence in the final model selected. However, in order to determine whether the functional form of the dose-response adequately describes the relationship between relative risk and continuous measures of cumulative exposure and cumulative smoking, a test of goodness-of-fit is necessary.

Lemeshow and Hosmer (1982) propose "chi-square-like" statistics involving the rank-ordered conditional probabilities of disease for logistic models. The statistical properties of these statistics have not been published, so their value is still somewhat questionable. Hosmer and Lemeshow (1983) recently attempted to extend these statistics to conditional logistic regression techniques, but as before their statistical properties are unknown. Schoenfeld (1978) proposed a test of goodness-of-fit of life table regression models based upon arbitrary division of the covariate and time space into a two-dimensional grid. Although he did derive the asymptotic
distribution of his statistic to be chi-square, the mathematically complex estimation procedures necessary for its use make his test impractical without specialized software.

A more reasonable approach was suggested by Tsiatis (1980) in which the joint covariate space is divided into K mutually exclusive categories. These K categories are represented in the model by K-1 indicator variables with the lowest category used as baseline, i.e., \( Z_i = 0, i = 1, \ldots, K-1 \). In this way no functional form is assumed in the relationship between relative risk and the covariates. The fit of a model including these K-1 dummy variables plus the dose-response terms is compared to that of the dose-response model by means of a likelihood ratio test. If their is no substantial improvement using the categorical model compared to the parametric model, one would conclude that the parametric model provided a good fit.

Accordingly, the members of the cohort were divided into 20 groups corresponding to five intervals of cumulative exposure and four intervals of cumulative smoking. The cutpoints were chosen arbitrarily but yet to ensure that at least one lung cancer death occurred in each category. The intervals chosen and their resultant risk estimates relative to the baseline category (less than 300 WLM and 10 or less pack-years) are given in Table 2.6. Each of the nineteen categorical variables produced risk estimates greater than 1.0 relative to the baseline category. They generally increased with increasing level of cumulative exposure or cumulative smoking. This also lends credibility to the appropriateness of a dose-response model.
These 19 categorical variables were then added to the three variable dose-response model. This permits a check for goodness-of-fit via a likelihood ratio test with 19 degrees of freedom. This is sometimes referred to as the method of deviance (Frome, 1983). That is, we are testing the fit of the dose-response model in each of the 19 categories associated with selected levels of radon exposure and smoking. The resulting asymptotic chi-square was 26.96, $p=0.11$, indicating a fairly good fit. The greatest departures from the dose-response model occurred in the highest cumulative dose category ($>2400$ WLM) where the model slightly underestimated the relative risk.

Using the dose-response model developed in this chapter, the underlying cancer mechanisms will be investigated in Chapter III. The multi-stage carcinogenesis model will be assumed and temporal relationships such as lagging, time since last exposure and various measures of age will be examined.
# TABLE 2.1

Regression Variables Considered in Development of Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Exposure</td>
<td>Working Level Months (WLM)</td>
<td>430.3</td>
<td>0.3-10,000+</td>
</tr>
<tr>
<td>Average Exposure Rate</td>
<td>WLM/month</td>
<td>10.3</td>
<td>0.03-998</td>
</tr>
<tr>
<td>Cumulative Cigarette Smoking*</td>
<td>Packs</td>
<td>10,027</td>
<td>0.0-61,000</td>
</tr>
<tr>
<td>Smoking Rate</td>
<td>Packs/day</td>
<td>0.64</td>
<td>0.0-3.5</td>
</tr>
<tr>
<td>Age at Initial Exposure</td>
<td>months</td>
<td>348.4</td>
<td>101-877</td>
</tr>
<tr>
<td>Calendar Year of Initial Exposure</td>
<td>year</td>
<td>1954</td>
<td>1908-1963</td>
</tr>
<tr>
<td>Birth Year</td>
<td>Calendar year</td>
<td>1921</td>
<td>1877-1948</td>
</tr>
<tr>
<td>Height</td>
<td>short (&lt;68 inches)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>medium (68-70 inches)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tall (&gt;70 inches)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of employment</td>
<td>Months underground</td>
<td>48.0</td>
<td>1-371</td>
</tr>
<tr>
<td>Years of Prior Hardrock Mining**</td>
<td>Years</td>
<td>0.0</td>
<td>0-42</td>
</tr>
</tbody>
</table>

*20.4 percent never smoked
**62 percent had no prior hardrock mining
TABLE 2.2
Mortality Experience of U.S. Uranium Miners
Cohort as of December 31, 1977

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>2390</td>
<td>71.4</td>
</tr>
<tr>
<td>Deceased (all causes)</td>
<td>957</td>
<td>28.6</td>
</tr>
<tr>
<td>Deaths from lung cancer</td>
<td>186</td>
<td>19.5</td>
</tr>
<tr>
<td>Deaths from all other causes</td>
<td>771</td>
<td>80.5</td>
</tr>
<tr>
<td>Total</td>
<td>3347</td>
<td>100.0</td>
</tr>
</tbody>
</table>
### TABLE 2.3

Results of Initial Model Including All Main Effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Exposure (WLM/1000)</td>
<td>0.272</td>
<td>0.057</td>
<td>4.764</td>
</tr>
<tr>
<td>Average Exposure Rate (WLM/month)</td>
<td>0.326</td>
<td>0.593</td>
<td>0.550</td>
</tr>
<tr>
<td>Cumulative Packs of Cigarettes (Packs/1000)</td>
<td>0.049</td>
<td>0.013</td>
<td>3.670</td>
</tr>
<tr>
<td>Cigarette Smoking Rate (Packs/day)</td>
<td>0.141</td>
<td>0.159</td>
<td>0.887</td>
</tr>
<tr>
<td>Age at first exposure (months)</td>
<td>-0.005</td>
<td>0.002</td>
<td>-1.981</td>
</tr>
<tr>
<td>Prior hardrock mining (Yes=1, No=0)</td>
<td>-0.044</td>
<td>0.153</td>
<td>-0.286</td>
</tr>
<tr>
<td>Height</td>
<td>-0.141</td>
<td>0.091</td>
<td>-1.542</td>
</tr>
<tr>
<td>Calendar year of first exposure</td>
<td>0.042</td>
<td>0.026</td>
<td>1.590</td>
</tr>
<tr>
<td>Duration of underground uranium mining (months)</td>
<td>-0.002</td>
<td>0.001</td>
<td>-2.799</td>
</tr>
</tbody>
</table>

Model Log likelihood = -1044.7
Model chi-square = 115.5, d.f.=9
### TABLE 2.4
Assessment of Effect Modification: Interaction Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Exposure (WLM/1000)</td>
<td>0.165</td>
<td>0.289</td>
<td>0.569</td>
</tr>
<tr>
<td>Cigarette Packs (PACKS/1000)</td>
<td>0.055</td>
<td>0.011</td>
<td>5.15</td>
</tr>
<tr>
<td>Age at First Exposure (AGE)</td>
<td>-0.004</td>
<td>0.002</td>
<td>-1.67</td>
</tr>
<tr>
<td>Height (HT)</td>
<td>-0.029</td>
<td>0.109</td>
<td>-0.26</td>
</tr>
<tr>
<td>Calendar year of first Exposure (YRST)</td>
<td>0.026</td>
<td>0.027</td>
<td>1.943</td>
</tr>
<tr>
<td>WLM X PACKS</td>
<td>-0.0008</td>
<td>0.006</td>
<td>-0.137</td>
</tr>
<tr>
<td>WLM X AGE</td>
<td>-0.0004</td>
<td>0.0004</td>
<td>-0.932</td>
</tr>
<tr>
<td>WLM X HT</td>
<td>-0.071</td>
<td>0.044</td>
<td>-1.66</td>
</tr>
<tr>
<td>WLM X YRST</td>
<td>0.009</td>
<td>0.006</td>
<td>1.56</td>
</tr>
</tbody>
</table>

Log likelihood = -1046.8  
Model chi-square = 110.9, d.f. = 9
### TABLE 2.5a

**Quadratic Model in Cumulative Exposure and Cumulative Smoking (8 yr. lag)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Std. Error</th>
<th>Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at 1st Exposure (mos.)</td>
<td>0.003</td>
<td>0.001</td>
<td>2.76</td>
</tr>
<tr>
<td>Cumulative Exposure (WLM/1000)</td>
<td>1.206</td>
<td>0.134</td>
<td>9.01</td>
</tr>
<tr>
<td>Cumulative Smoking (Packs/1000)</td>
<td>0.131</td>
<td>0.025</td>
<td>5.33</td>
</tr>
<tr>
<td>(WLM)$^2$</td>
<td>-0.117</td>
<td>0.021</td>
<td>-5.49</td>
</tr>
<tr>
<td>(PACKS)$^2$</td>
<td>-0.002</td>
<td>0.001</td>
<td>-2.77</td>
</tr>
</tbody>
</table>

Log-likelihood = -1025.71  
Model chi-square = 171.6, d.f. = 5

### TABLE 2.5b

**Model Using Natural Logarithms of Cumulative Exposure and Cumulative Smoking Plus Their Backgrounds* (8 yr. lag)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Std. Error</th>
<th>Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at First Exposure</td>
<td>0.002</td>
<td>0.001</td>
<td>2.64</td>
</tr>
<tr>
<td>Log (Cumulative Exposure + Background)</td>
<td>0.635</td>
<td>0.067</td>
<td>9.52</td>
</tr>
<tr>
<td>Log (Cumulative Smoking + Background)</td>
<td>0.389</td>
<td>0.068</td>
<td>5.72</td>
</tr>
</tbody>
</table>

Log-likelihood = -1025.83  
Model chi-square = 171.4, d.f. = 3

*Cumulative exposure background = 0.2 WLM/year  
Cumulative smoking background = 0.005 packs/day
Risk relative to lowest category (>300 WLM and less than 10 pack-years of smoking) adjusted for age

<table>
<thead>
<tr>
<th>Pack-Years</th>
<th>L.C.Deaths RR</th>
<th>L.C.Deaths RR</th>
<th>L.C.Deaths RR</th>
<th>L.C.Deaths RR</th>
<th>L.C.Deaths RR</th>
<th>L.C.Deaths RR</th>
<th>L.C.Deaths RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0-10</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>3.0</td>
<td>4.0</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>0-300</td>
<td>2.0</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
<td>4.0</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>500-600</td>
<td>2.0</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
<td>4.0</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>1200-2400</td>
<td>2.0</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
<td>4.0</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>&gt;2400</td>
<td>2.0</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
<td>4.0</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>40-69.5</td>
<td>4.0</td>
<td>6.0</td>
<td>9.0</td>
<td>13.0</td>
<td>21.0</td>
<td>37.0</td>
<td>83.0</td>
</tr>
<tr>
<td>70</td>
<td>13.0</td>
<td>21.0</td>
<td>37.0</td>
<td>83.0</td>
<td>200.0</td>
<td>350.0</td>
<td>890.0</td>
</tr>
<tr>
<td>115-14.8</td>
<td>14.0</td>
<td>24.0</td>
<td>44.0</td>
<td>91.0</td>
<td>220.0</td>
<td>400.0</td>
<td>980.0</td>
</tr>
<tr>
<td>&gt;40</td>
<td>24.0</td>
<td>44.0</td>
<td>91.0</td>
<td>200.0</td>
<td>400.0</td>
<td>1000.0</td>
<td>2500.0</td>
</tr>
</tbody>
</table>

Cumulative lifetime radon exposure (W.L.M.).

Relative risk and number of lung cancer deaths by radon and smoking category

Table 2.6
Figure 2.1

Levels (0.2 WLM/year) with similar smoking histories

Hazard Rate Ratio Relative to Miners Exposed to Background

Cumulative Exposure (WLM)

--- 95% Confidence Limits

Exposure to Radon Daughters (LAE=6 years)

Relative Risk as a Function of Cumulative Exposure
CHAPTER III

Temporal Aspects of Risk Assessment Models

3.1 Introduction

There are many obstacles confronting the analyst who attempts to produce a valid and credible quantitative risk model. Among the most difficult problems associated with this goal is the proper assessment of the many temporal factors affecting the exposure-disease relationship. Such variables as latent periods, duration of exposure, calendar time, age at first exposure and time since last exposure all must be carefully considered in analyzing data from a longitudinal study. The complexity of such a task is compounded by the fact that all such temporal variables are highly intercorrelated and many of them are censored as well.

In this chapter methods are discussed for addressing the effect of temporal factors, and suggestions are made concerning which methods work best. In addition, the effects of such variables as age at first exposure time since last exposure will be shown to be important to the understanding of the underlying cancer mechanism as postulated by the multistage model.
3.2 The Effect of Latency

Lung cancer is known to have a relatively long latency period. Latency period is defined in this study to be the time from initial exposure to death from carcinoma of the lung. Various estimates as to the length of latency after exposure to ionizing radiation have been proposed, ranging from 10 to over 25 years (Beir III, 1980). These estimates are all made for initiators of the cancer cells. Some have proposed that, once initiated other carcinogens may act as promoters (Lundin, et al, 1979) serving to accelerate the clinical appearance of tumors. If one assumes some form of the multistage model as proposed by Armitage and Doll (1961), the initiators would be acting at early stages while the promoters would be more effective in the later stages. Since cigarette smoking has been suggested as both an initiator and a promoter, (Doll and Peto, 1978) and the stage at which radon acts is a matter of some debate, it would not seem wise to assume a lengthy latency period for either of these exposures. On the other hand, it is clear that exposures to either radon or smoking in the last few years immediately prior to death were not influential in tumor development. In fact, dose-response relationships in lung cancer studies which do not hold after lagging exposure would seem to have little credibility (Gilbert, 1979).

Some idea of the latency period in this cohort can be seen by examination of the frequency distribution of lung cancer deaths over time since first exposure. Few deaths occur before 10 years of exposure, with the median in the 15-20 year range, as of the end of
1977. If the exposure effective in initiating cancer does not always occur at the time of first underground uranium mining, the true biological latency period would be somewhat shorter than indicated by the data in Figure 3.1. In fact, the "true" biological latent period resulting from exposure to a given carcinogen is actually unobservable in any study in which exposure and follow-up overlap.

3.2.1 Lagging Exposure

Lagging is a method of dealing with ineffective or redundant exposures, i.e., those accumulated in years immediately prior to death. The assumption is that once transformed cells have reached a certain stage additional exposure has no effect upon the outcome. Although the concept of lagging is related to latency, they are not equivalent. Some of the exposure after a cancerous tumor has been initiated may be effective in accelerating tumor growth. Since we are dealing with a dynamic process which involves censored observations, the effect of additional exposure may be to produce additional lung cancer mortality prior to the end of follow-up. Therefore, it is important to consider the stage of cancer development affected by the exposure in choosing the appropriate lag.

The minimum lag appropriate for removing redundant exposure apparently is two years. This is the survival time reported by Doll and Peto (1976) after clinical detection of lung cancer in male British doctors. Whittemore and McMillan (1983) chose a ten year lag for both cigarette smoking and radon exposure in their case-control analysis of
the U.S. uranium miners. This choice was made for two reasons: To avoid any bias in estimation of cumulative exposure for those miners serving past 1969 (the last time exposure was updated), and because of an estimated average of 10 year between malignant cell transformation and clinical diagnosis of lung cancer given by Geddes (1979).

Lagging exposure may be thought of as a special form of weighting function over the period of accumulating exposure. The weighting function for lagged exposure takes the form illustrated in Figure 3.2.

Thus the cumulative lagged exposure $LE(t)$ at any year $t$ prior to death can be expressed as the sum of terms involving the product of the weighting function $W(t)$ and measured cumulative exposure $CE(t)$ at each year $i$ of follow-up:

$$LE(t) = \sum_{i=1}^{t} W(t-i+1)CE(i)$$

where $W(t)=0$ for $t<L$

$W(t)=1$ for $t>L$

and $L=\text{lag period.}$

If the lagged exposure is a continuous function of time since initial exposure, the relationship can be expressed as:

$$LE(t) = \int_{0}^{t} W(t-x)CE(x)dx$$

In order to avoid a somewhat arbitrary choice of $L$ for this analysis, lags ranging from 0 to 12 years in two year intervals were
used. The degree of fit as measured by the likelihood of the model
(twice the difference in log-likelihood from the null model) is
plotted in Figure 3.3. The power model given in Table 2.5b involving
cumulative exposure, cumulative smoking and age at initial exposure was
used for all lags. In addition, the coefficient associated with
cumulative radon exposure and cumulative cigarette smoking are plotted
versus lag in Figure 3.4 to provide an assessment of the effect of
different lags upon risk estimates.

Examination of Figure 3.3 indicates that a lag of 6 years for
both radon exposure and cigarette smoking provides the best fit to the
data. As mentioned earlier, there is an implicit eight year lag
between end of follow-up (Dec., 1977) and last measured exposure (1969)
for anyone surviving 1977. However, even though a six year lag is two
years short of this, it should produce very minimal bias. This is
because few members of the cohort were still mining uranium in 1975
(<10 percent) and their exposures were orders of magnitude less than
exposures earlier in the study (Lundin et al., 1971).

The effect of lagging upon the estimated relative risk of lung
cancer is illustrated in Figure 3.4. As the lag time increases the
relative risk per unit WLM monotonically decreases, although all
coefficients remain statistically significant. The implication here is
that lagging exposure has a relatively stronger effect on cumulative
exposure for lung cancer cases than the members of their age-matched
risk sets. The practical consequence of this is that the relative risk
estimate for exposure to radon is dependent upon the appropriate
selection of a lagging period. The same was not true, however, for
risk due to cigarette smoking. The relative risk of lung cancer from smoking was invariant to changes in length of lag time. The parameters of the model for three exposure weighting schemes are given in Table 3.1.

The estimates reported above were obtained by lagging both radon exposure and pack-years of cigarette smoking for the same period of time. Since smoking and radon daughters may act at different stages of cancer development, it seemed prudent to try different lag periods for smoking and radon exposure. Several such models were produced by lagging radon daughter exposure and cigarette smoking in various lags of from 2 to 10 years. Results indicated neither a significant change in fit nor in risk estimates from models where both exposures were lagged equally. This is not unexpected considering the insensitivity of estimated smoking risk to changes in lag time seen in Figure 3.4.

3.2.2 Partial Weighting Schemes

The most popular method of weighting exposure is lagging by the function illustrated in the previous section (Figure 3.2). Undoubtedly one of the reasons for this is its computational simplicity and ease of interpretation. Implicit in the use of this technique is the assumption that at some point in time the exposure suddenly changes from fully effective to completely ineffective. This step function is actually an approximation to a more realistic weighting function which gradually changes from effective to ineffective during some period of time.
Land (1976) proposed a partial weighting of exposures which increased linearly over the follow-up period in an analysis of risk from coke oven effluents. Mazumdar and Redmond (1979) in collaboration with Land combined Land's approach with various lagging periods. Their weighting functions were of the form illustrated in Figure 3.5.

Their approach seems reasonable in that redundant exposure occurring after clinical evidence of lung cancer but before death would be completely eliminated. However, exposure before that point would gradually increase in effectiveness in periods farther from death in accordance with the assumption of a long latency period. Unfortunately, they never indicated which of these weighting schemes they preferred. Instead they made relative risk estimates for various combinations of lag and partial weighting, noting that a 15 year lag followed by partial weighting produced slightly higher relative risk estimates than partial weighting with no lag.

A similar strategy was employed using the uranium miner data. Since the best fitting lag periods were in the 2-6 year range, partial weighting schemes were employed using a 2-6 year lag followed by a linearly increasing weight for the next 6-8 years. All of these combinations fit very well, with little difference in log-likelihoods (maximum difference = 1.4). The various partial weighting combinations generally produced slightly better fits than lagging alone. The coefficient for cumulative radon exposure estimated by using a lag of L years followed by a partial weighting for P years was very similar to that produced by simply lagging for L years. The combination producing the highest likelihood ratio statistic was a lag of four years followed
by partial weighting for the next six years. All exposures received 10 years prior to death from lung cancer received a weight of 1.0 (assumed to be fully effective). This approach not only produces a good-fitting model but seems to be biologically plausible in view of estimated latency periods for lung cancer and the complete redundancy of exposures received in the few years immediately prior to death. Table 3.1 presents the resulting coefficient estimates for lagging 4 years and partial weighting the next 6 years compared to the best-fitting lag of 6 years.

3.2.3 Weighting by Distribution Functions

To this point proposed weighting models have only addressed the issue of the diminishing effectiveness of exposures received in a period of time proximate to death. However, there is evidence (Bizzozero, et al. 1966) to suggest that the effectiveness of radiation exposure peaks and then declines after a period of time. That is, if one survives exposure for a long period of time the effectiveness of those early exposures on current risk decreases. Lundin (1971) proposed the use of a lognormal distribution function to weight those exposures most heavily which occurred approximately 10 years prior to death, with weights decreasing for periods either close to or very far from the time of death. Figure 3.6 illustrates the form of such a weighting function with a median of 10 years and a dispersion factor (geometric standard deviation) of 1.5. In this weighting scheme, the weight for the jth year of exposure is the area under the lognormal
curve from \( j-1 \) to \( j \) years. Since the maximum weight for any year of exposure never exceeds 0.11 when using this weighting function, the resulting effective cumulative exposures are usually less than the average exposure received during one year. For example, if one were evaluating the effective exposure for a miner 20 years after initial exposure who had received 10 WLM/year for 10 consecutive years the result would be:

\[
\int_{0}^{20} W(20-x)CE(x)dx = \sum_{i=1}^{20} W(20-i+1)CE(i)
\]

\[= (0.013)(10.0) + (0.017)(10.0) + \ldots + (0.0001)(0.0)\]

\[= 4.59 \text{ WLM}\]

where \( CE(i) \) is the cumulative exposure in year \( i \) and \( W(i) \) is the weight for year \( i \). By contrast, the estimated effective cumulative exposure for the same miner using a lag of 10 years or less would be 100 WLM. With weighted cumulative exposures at these low levels it is not surprising that Lundin estimated a 12 percent increase in relative risk per "effective" WLM. Lundin's estimate is approximately 10 to 40 times higher than estimates by Waxweiler, et al. (1981) and Whittemore and McMillan (1983), respectively, using more recent updates of the same data.

Although use of a lognormal weighting function has a certain intuitive appeal and has often been cited as a possible alternative to simple lagging, its use in quantitative risk assessment appears unreasonable. If the shape of the curve is retained but the amplitude is shifted upward so that the maximum is 1.0, the results may be more
realistic. Also, if the objective is simply to investigate the shape of the dose-response function, the log normal weighting function may be of value. Caplan (1982) used lognormal weighting of exposures to arsenic in such a way. He found that the shape of the dose-response was essentially unchanged from that produced by a simple 10 year lag. The risk estimates, however, were not comparable.

Since the quantitative results with a distributional form of weighting function appear to have little credibility, this technique will not be used. Even if the magnitude of the weights were adjusted upward, the computational complexity of such a weighting scheme makes it unfeasible for any cohort without extremely long follow-up. For a study in which the risk of cause-specific mortality has peaked, this approach may be viable.

3.3 Temporal Component of Cumulative Exposure

One of the most important goals in constructing a valid risk assessment model is establishing the appropriate exposure index. When no measures of the concentration levels of a given agent are available (as is often the case with retrospective studies), duration of time spent in "exposed" job categories is frequently used as a surrogate for exposure. However, when industrial hygiene data are available characterizing variations in concentration levels over time, the exposure index generally used is cumulative exposure. Although this index of exposure is meaningful and often produces good-fitting models, it is sometimes unclear whether it adequately addresses the complete
exposure-disease relationship. The obvious problem with using cumulative exposure is that low exposures accumulated over long periods of time are assumed to be etiologically equivalent to high exposures for short periods of time. In general, cumulative exposure is actually the product of duration and average intensity of exposure.

Doll and Peto (1978) examined the effects of cigarette smoking in British physicians on lung cancer incidence. They found that the incidence of lung cancer was proportional to the product of the 4th or 5th power of duration and only the second power of intensity (smoking rate). If these findings apply to other carcinogens, it is not surprising that an exposure rate effect may often be obscured in epidemiologic studies by a much stronger dependence on duration of exposure. Average exposure rate was found to be statistically non-significant when it was included in a model already containing cumulative exposure (Table 2.3). Since cumulative exposure is highly correlated with duration of exposure, it is possible that the strong dependence of lung cancer risk on duration obscures the effect of exposure rate. This may be especially true when duration of mining is defined to be the length of time between initial exposure and end of employment in uranium mining (as was the case in analyses in Chapter II). Employment in uranium mining was extremely cyclical for most men in the cohort, with long periods of time often elapsing between exposures. A better measure of duration of exposure may be the actual time spent underground in uranium mining. Accordingly, a new definition of exposure rate was made:

\[ \text{RATE}(t) = \frac{\text{WLM}(t)}{\text{UGMON}(t)}, \]
where $WLM(t)$ is cumulative exposure and $UGMON(t)$ is the total number of months underground at age $t$. Defined in this way, exposure rate is the average monthly $WLM$ received while actually mining.

When this time-dependent variable was added to the model including age at initial exposure, log of cumulative exposure and log of cumulative smoking, a surprising difference was found from earlier results. Now exposure rate was highly significant but with a negative coefficient: $\beta = -0.019$, chi-square $= 6.60$, $p = 0.01$. Since exposure rates were highly skewed to the right, the natural logarithm of RATE was substituted. Results were even stronger: $\beta = -0.314$, chi-square $= 13.1$, $p < .001$. The implication of this result is that lower exposure rates for longer periods of mining are more hazardous than higher rates for shorter periods of time when each work history produces the same cumulative exposure. Specifically, a miner accumulating a given total $WLM$ in twice the amount of time as a miner of the same age with the same cumulative total has $2^{-0.314} = 0.24$ or $24$ percent higher risk of death from lung cancer. This result agrees with many animal carcinogenesis studies which indicate low dose rates are more effective than high dose rates per unit of dose (Druckrey, 1967). Similar results were also found in an earlier non-time-dependent analysis of this data by Hornung and Samuels (1981).

Another possible way of assessing the effect of exposure rate upon the risk of lung cancer is to break cumulative exposure into its
two constituent parts. Any miner's cumulative exposure WLM(t) at age t can be expressed as:

\[ WLM(t) = RATE(t) \cdot UGMON(t) \]

or

\[ \ln(WLM(t)) = \ln(RATE(t)) + \ln(UGMON(t)). \]

Since multiplicative models are being used, we may remove WLM(t) from the dose-response model and substitute RATE(t) and UGMON(t) or their logarithms. Several forms of this model were run but results of all of them indicated substantially poorer fits to the data than those obtained using cumulative exposure alone. This approach, therefore, reveals no additional information concerning the effect of exposure rate.

3.4 Implications of the Multistage Carcinogenesis Model

In order to investigate the risk of carcinogenesis as influenced by exposure to a given agent, it is necessary to understand the underlying biologic mechanisms. In the last two decades much attention has been given to a general statistical model of cancer development usually referred to as the multistage model (Armitage and Doll, 1961). It assumes that the production of a cancerous cell depends upon its undergoing k distinct changes in sequence. Any or all of these k changes may be influenced by the concentration in the tissue of a particular carcinogen. After transformation through all k stages, the cancerous cell produces a tumor by rapid cell division. This period of time is generally referred to as the induction period while the former is referred to as the transformation period. In the absence
of any specific carcinogenic exposure, the age specific background incidence rate \( I(t) \) is given by:

\[
I(t) = \alpha_1 \alpha_2 \ldots \alpha_k
\]

where \( \alpha_i \) are rate parameters associated with each of the \( k \) stages. Assumptions of this model are that \( \alpha_i \) are independent of age and the induction time is negligible compared to the individual's age \( t \).

Whittemore (1977) assumed that in the presence of a concentration \( c(t) \) of a carcinogen the transformation rates become \( \alpha_i + \beta_i c(t), i = 1, \ldots, k \). Her model was developed assuming only one of the \( k \) stages was affected by exposure to the carcinogen. Later Day and Brown (1980) extended this model to allow effects at multiple stages. These multistage models indicate that the temporal pattern of excess cancer incidence is dependent upon the stage or stages affected by exposure. Therefore, if one subscribes to some form of the multistage model, it should be possible to predict which stage(s) are affected by careful examination of the temporal patterns of excess cancer risk.

3.4.1 Effect of Age at Exposure

Brown and Chu (1982) investigated the implications of the multistage model under certain fixed (but often unrealistic) conditions. They assumed that exposure was received at a constant rate \( c \) so that duration of exposure \( d \) is actually directly proportional to cumulative exposure. They found that when using a relative risk model, \( RR \) is a decreasing function of age at initial exposure when only the first stage is affected, but an increasing function of age at initial exposure when the penultimate (\( k-1 \)st stage) is affected.
Day and Brown (1980) used the multistage model to predict the effect on relative risk of age at initial exposure. They assumed a five stage model, fixed duration of exposure at five years, and then plotted the RR curves for a carcinogenic effect on stages one through four (penultimate). Figure 3.7 illustrate the shape of such predicted RR curves for age at initial exposure.

Whittemore (1977) developed a version of the multistage model in order to look at three exposure scenarios: single exposure at one point in time, continuous exposure at a constant rate, and exposure at varying intensities. When considering exposure of varying intensity (the usual occupational situation) she found that increasing age at initial exposure produced decreasing or constant relative risks if the first stage was affected and increasing RR when a later stage was affected.

In addition to examination of age at initial exposure, Thomas (1982) considered the effect of age at termination of exposure for varying durations. He concluded that the shape of the dose response curve depended upon the stage at which the carcinogen acts as well as the choice of age at first or last exposure for inclusion in the model. Relative risk was most heavily influenced by age at last exposure for a late stage carcinogen and was an increasing function of that age.

Therefore, if an effect upon one stage of the multistage model is assumed, it should be possible to predict whether an early or late stage is affected, by examination of the coefficient for age at initial exposure and age at termination of exposure in the Cox model. The
coefficient of AGE1 in the model was positive (β=0.0026) and highly significant (P=0.004). Figure 3.8 illustrates the effect on relative risk of age at initial exposure compared to a miner beginning work at age 15. For comparison the effect of age at start of cigarette smoking relative to someone starting at age 15 was also plotted. This estimate was based on an analysis of smokers and produced a negative but non-significant coefficient (β=-0.002, P=0.22). The curve associated with radon daughter exposure is similar in shape to the one predicted by Day and Brown in Figure 3.7 for a carcinogen affecting the penultimate stage. The curve associated with cigarette smoking, on the other hand, is more similar to that associated with an effect upon an early or intermediate stage.

When age at termination of underground mining (AGESTOP) was added to the model a similar significant positive effect was found (β=0.003, P=.01). Once again, this effect would be indicative of a late stage carcinogenic effect of radon daughters.

3.4.2 Effect of Time Since Termination of Exposure

The easiest way to study the underlying carcinogenic mechanisms at work in a population is to have a situation where all exposure occurs at one point in time (A-bomb studies) or occurs at a constant rate for a fixed period of time (most animal studies). However, when faced with occupational exposure patterns of varying intensity, one may still make some valid inferences by examining the effect of cessation of exposure.
Day and Brown (1980) predicted the effect on relative risk of time since exposure stopped when a multistage model is assumed. They found that when exposure begins sometime after infancy excess relative risk increases, peaks and then decreases with time since termination of exposure when the first stage is affected. When the penultimate stage is affected relative risk strictly decreases with time after last exposure. Figure 3.9 illustrates their predictions for the first four stages of a five stage model assuming an exposure duration of five years.

In order to investigate the effect of termination of exposure, all miners were identified who had indicated during the course of follow-up that they had retired from uranium mining. Approximately 95 percent of the miners had retired for more than one year prior to the end of follow-up. The average time since last exposure was 14.3 years for those miners not dying of lung cancer and 7.1 years for lung cancer cases.

The time in months since last exposure was then entered as a time-dependent covariate in the original model containing log of exposure, the log of smoking, and age at initial exposure. The estimated coefficient for this term was negative and highly significant ($\beta=-0.005$, chi-square=14.2, $P<.001$). This implies that the risk of death from lung cancer 10 years after mining uranium is $\exp(-0.005\times120)=0.542$ relative to a miner still mining with the same cumulative exposure, smoking history, and age.

This would not seem to be an artifact of leaving employment after diagnosis of lung cancer since this form of cancer is rapidly
fatal and average time since last exposure was over 7 years. A result such as this would be associated with an effect upon the penultimate stage of carcinogenesis. Similarly, time since quitting smoking for ex-smokers was entered into the model with non-smokers excluded. The estimated coefficient for this term was positive but not statistically significant ($\hat{\beta}=0.0003$, chi-square $= 0.10$, $P=0.75$). This result is in contrast to the decreasing risk found in ex-smokers by Doll and Reto (1976). Their study, however, was presumably free of high exposures to other lung carcinogens.

The change in relative risk with increasing time since exposure is plotted in Figure 3.9 for both radon daughters and cigarette smoking. As was the case with age at initial exposure, the curves relating excess relative risk to time since last exposure are very similar in shape to that predicted by a multistage model with radon daughters exposure acting at the penultimate stage and cigarette smoking at an intermediate stage.

3.5 Summary and Discussion

We have examined the various temporal factors affecting quantitative risk assessment models, including weighting exposure over time, duration of exposure, calendar time, age at first exposure, and time since cessation of exposure. In order to quantify risk it is important to attempt to identify the appropriate index of exposure. In this cohort cumulative exposure seems to be a better predictor of risk than either of its components: duration of employment and rate of
exposure. However, there is evidence to suggest that for a given level of cumulative exposure, lower exposure rates are more effective per WLM than higher rates.

Various time-exposure weighting schemes were employed with a four year lag followed by a linear partial weighting of the next six years providing a good fit. Although the fact that this scheme fits the data well does not mean that it is correct, there is biological plausibility in its use. Four years is within the range of induction times from inception of tumor until death. Therefore elimination of all exposure within a minimum of four years prior to death seems reasonable. The partial weighting for the preceding six years is in agreement with a proposed 10 year median latency period (Lundin et al. 1971), while more realistic than a simple 10 year lag.

If some form of multistage carcinogenesis model is hypothesized, it is possible to predict the stage affected by radon daughter exposure. Since excess relative risk is an increasing function of age at initial exposure, we conclude that a later stage, possibly the penultimate, has been affected. The biological interpretation is that as a person ages more cells are transformed through the early stages either spontaneously or through background exposures. Therefore, at later ages there are more candidate cells available for late stage exposure-induced transformation. Although age at start of cigarette smoking is not significantly related to excess relative risk, the negative direction of the effect would suggest an effect on an intermediate to early stage. Similar conclusions are reached by examining time since last exposure. Since excess relative
risk decreases with time since termination of radon daughter exposure, a late stage is implicated.

Another reason to conclude that smoking and radon exposure act at different stages is the good fit of a multiplicative model. Both Lundin et al., (1971) and Whittemore and McMillan (1983) found a poor fit to this data for the additive model. In using mathematical models to simulate multistage carcinogenesis, Thomas (1982) found that interactions between co-carcinogens will tend to be additive if both act at the same stage and multiplicative if each acts at a different stage. They also found that if exposure to two carcinogens is spaced apart in time (as is smoking and radon exposure in most miners) the combined effect has the greatest synergy.

These conclusions have potential public health implications. If indeed exposure to radon daughters acts on a late stage of a multistage carcinogenic process, the implication is that removal of exposure is beneficial to the health of the individual. Those surviving ten years outside the uranium mines have their lung cancer risk reduced by approximately 50 percent. However, if radon acted at an early stage the situation would be more dangerous since risks of lung cancer would continue to rise for many years and miners exposed while young would be at the highest risk. Therefore, if someone must mine uranium, he should begin at an early age and work underground for a relatively short time before being transferred to a topside job.
The next chapter addresses the difficult problem of errors in individual exposure estimates. We know that substantial errors exist in assignment of exposure over time to each miner in the cohort. Chapter IV examines the magnitude and distribution of such errors and proposes a method for adjusting relative risk estimates in their presence.
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<th>Std. Error</th>
<th>Lag=6 Coefficient</th>
<th>Std. Error</th>
<th>Lag=4, Partial Weighting 4-10 Years Coefficient</th>
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<td>0.7404</td>
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<tr>
<td>ln(Packs)</td>
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<td>0.0681</td>
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<td></td>
<td>187.9</td>
<td></td>
<td>186.8</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3.1

Since initial exposure to radon daughters, distribution of lung cancer deaths as a function of time.
FIGURE 3.7
EFFECT OF AGE AT INITIAL EXPOSURE ON A MULTISTAGE MODEL

FIGURE 3.9
EFFECT OF CESSATION OF EXPOSURE ON A MULTISTAGE MODEL
FIGURE 3.8

Effect of age at initial exposure on risk relative to miner beginning at age 15 years.
FIGURE 3.10

Effect of time since last exposure on excess relative risk.
CHAPTER IV

EFFECTS OF ERRORS IN EXPOSURE MEASUREMENT ON RELATIVE RISK ESTIMATES

4.1 Introduction

Statistical interest in the subject of errors of measurement can be traced back at least as far as a 1902 paper by Pearson. He examined errors in measurement of a known quantity due to observational differences among a group of persons. He introduced such notions as a variable bias and correlation among independent measures.

Econometricians have struggled for years to find appropriate methods for dealing with errors of measurement in assessing the relationship between sets of variables. Similar problems have confronted those doing research in sociology and psychology where measures of people's behavior, opinions and feelings are notoriously difficult to obtain.

The 1968 paper by Cochran "Errors of Measurement in Statistics" provided a review of past work in this area. Cochran centered his attention on the type of mathematical model used to represent errors of measurement, their effect upon the precision and bias of statistical estimates, and procedures to remedy such consequences. He concluded that measurement errors often seriously compromise the results of standard statistical techniques, while at other times the effect is
negligible. The magnitude of the effect depends upon the size of error variances and also the correlation of the true value with the measured values.

There has been considerable work in the area of misclassification errors and their effect upon relative risk estimates in epidemiologic studies. Bross (1954) originally considered the effect upon estimation of the difference between two proportions when misclassification was the same for the two comparison groups. Keys and Kihlberg (1963), Fleiss (1973) and others showed that non-differential misclassification (sensitivity and specificity equal in both comparison groups) leads to underestimation of relative risk. They pointed out, however, that if the pattern of misclassification differed between comparison groups either overestimation or underestimation of relative risk was possible. In a more recent paper Copeland, et al. (1977) again found that non-differential misclassification in $2 \times 2$ tables produced relative risks biased towards the null value. They found that the magnitude of bias was a function of sensitivity (correct identification of positives) and specificity (correct identification of negatives). In cohort studies the bias was primarily dependent on specificity, while in case-control studies sensitivity was more important. They also reaffirmed the variable direction of bias with differential misclassification.

Very little work has been done concerning the effects of errors on ordinal or continuous measures of exposure. Prentice (1982) examined the effect upon the Cox model of errors in covariate measurement. He introduced the conditional expectation of the hazard $\lambda(t, z, x)$ for true values of covariates $z$ given measured values $x$ and
survival to time \( t \). The basic assumption necessary for validity of this approach is the conditional independence of \( \lambda(t, z, x) \) and \( x \), given the true value \( z \). That is, the observed covariate \( x \) can have no predictive value given the true value \( z \). The work of Prentice will form the basis for examination of the effect of covariate error on relative risk estimation using the Cox model, assuming various forms of the risk function as well as the distribution of error in the covariate(s).

4.2 **Conditional Expectation of the Hazard Function**

The standard Cox model is assumed to be appropriate:

\[
\lambda(t; z) = \lambda_0(t) \exp(\beta z(t))
\]

where \( \lambda_0(t) > 0 \) is an arbitrary baseline hazard function, \( z(t) \) is a vector of covariates which may or may not be time-dependent, and \( \beta \) is a vector of coefficients to be estimated. Now suppose that instead of the "true" covariate \( z(t) \) only an estimate or measured value \( x(t) \) is available. The objective is still to estimate the coefficients \( \beta \) associated with the \( z(t) \). However, direct estimation of \( \beta \) associated with \( z \) in the usual maximum likelihood sense would not be possible due to the measurement errors in \( x(t) \).

Under conditional independence of the hazard rate and \( x(t) \) given the true value \( z(t) \) the hazard function can be written:

\[
\lambda(t; z(t), x(t)) = \lambda(t; z(t)).
\]

Prentice notes that the relationship is equivalent to assuming that the measured covariate \( x(t) \) has no predictive value when the true value \( z(t) \) is known, which seems very reasonable in most situations.
The hazard function of the measured covariates \( x, \lambda(t;x(t)) \), can be written as the conditional expectation of \( \lambda(t; z(t), x(t)) \) given survival to time \( t \) and \( x(t) \). This can be written as:

\[
\lambda(t; x(t)) = E[\lambda(t; z(t), x(t)) | T > t, x(t)]
\]

If the conditional independence assumption is invoked the result is:

\[
\lambda(t; x(t)) = E[\lambda(t; z(t)) | T > t, x(t)]
\]

Therefore, the Cox model as a function of the measured covariates \( x(t) \) is:

\[
\lambda(t; x(t)) = \lambda_0(t) E[\exp(a z(t)) | T > t, x(t)]
\]

The inclusion of \( T > t \) in the conditional expression is somewhat troublesome. It may be eliminated in the conditional expectations if either \( P(T > t | z(t)) \approx 1 \) for the period of follow-up or if the distribution of \( z(t) \) given \( x(t) \) does not change substantially over the period of follow-up. The latter assumption seems valid as will be shown in section 4.4. The assumption that \( P(T > t | z(t)) \approx 1 \), while probably mildly violated for heavily exposed miners in this study, will often be valid for large cohorts and rare diseases.

Prentice points out that the validity of the partial likelihood specification of Cox (1975) makes necessary some assumption regarding the censoring mechanism. The most convenient assumption asserts that a subject at risk at time \( t \) with measured covariate \( x \) can be regarded as representative of the population without failure at time \( t \) with covariate value \( x \). Since over 70 percent of the cohort survived the period of follow-up and most mortality (other than lung cancer) is apparently unrelated to radon daughter exposure (Waxweiler et al., 1981) this assumption seems reasonable.
4.3. **Estimation of $\beta$**

4.3.1. **Log-linear Risk Function**

For simplicity of notation, consider only a single covariate $z(t)$. Since the objective is to estimate $\beta$ (and equivalently the relative risk) for the true covariate $z(t)$ when only a measured value $x(t)$ is available, the expectation $E[\exp(\beta z(t))|x(t)]$ must be specified as a function of $\beta$. The expectation can be written:

$$ \int_{-\infty}^{\infty} \exp(\beta z(t)) f(z(t)|x(t)) dz $$

where $f(z(t)|x(t))$ is the density function for the conditional error distribution of $z(t)$ given the measured value $x(t)$. This is simply the moment generating function for the distribution $f(z|x)$. Therefore most distributions with an exact moment generating function could be used to estimate $\beta$, assuming that the distribution is an adequate model for the error distribution for covariate $z(t)$.

As an illustration, assume that the distribution of $z(t)$ given $x(t)$ is normal with mean $\mu$ and variance $\sigma^2$. Also assume that the error distribution does not change over the period of follow-up. Then:

$$ \lambda(t;x(t)) = \lambda_0(t) E[\exp(\beta z)|x] $$

$$ = \lambda_0(t) \int_{-\infty}^{\infty} \exp(\beta z) f(z|x) dz $$

$$ = \lambda_0(t) \int_{-\infty}^{\infty} \exp(\beta z) \frac{1}{\sqrt{2\pi}\sigma} \exp(-\frac{(z-\mu)^2}{2\sigma^2}) dz $$

$$ = \lambda_0(t) \exp(\beta \mu + \frac{\beta^2 \sigma^2}{2}). $$
Prentice assumed $E(z|x)=\mu=x$. This is a reasonable assumption whenever the measured covariate is actually an average concentration measured in some work area at time $t$ which is assigned to all those working in that area at that time. This is exactly the case with the U.S. uranium miners since each miner's exposure was assigned from measured levels of radon daughters in the mine or mines in which he worked during a given year. It should be noted that assuming $E(z|x)=x$ essentially ignores environmental sampling variability since the measured level $x$ is assumed to be an accurate estimate of the true average exposure level for a given mine.

The degree to which true individual exposures vary about the measured levels in the mines determines the magnitude of $\sigma^2$. It seems reasonable to assume that the variance would be some function of $x$. Three cases will be examined where $\sigma^2=g(x)$. In all subsequent cases assume $E(z|x)=x$. Note also that the true risk function is assumed to be $\exp(\beta z(t))$.

Case 1: $\sigma^2=k>0$ (constant)

$$
\lambda_0(t)E[\exp(\beta z(t))] = \lambda_0(t)\exp(\beta x(t)+\beta^2\sigma^2/2) \\
= \lambda_0(t)\exp(\beta x(t)+\beta^2k/2) \\
= \lambda_0(t)\exp(\beta^2k/2)\exp(\beta x(t)) \\
= \lambda_0(t)\exp(\beta x(t))
$$

Therefore, in the situation where the variance is constant, $\beta$ would be correctly estimated when using the measured value $x(t)$. However the
underlying hazard $\lambda_0(t)$ would be inflated by the factor $\exp(\beta^2 k/2)$.

Case 2: $\sigma^2 = kx$

$$\lambda_0(t)E[\exp(\beta z(t))] = \lambda_0(t)\exp(\beta u + \beta^2 \sigma^2/2)$$
$$= \lambda_0(t)\exp(\beta x(t) + \beta^2 kx(t)/2)$$
$$= \lambda_0(t)\exp((\beta + \beta^2 k/2)x(t))$$
$$= \lambda_0(t)\exp(\beta^2 x(t))$$

In this case $\beta$ would be strictly overestimated by the term $\beta^2 k/2$.

Case 3: $\sigma^2 = kx^2$

$$\lambda_0(t)E[\exp(\beta z(t))] = \lambda_0(t)\exp(\beta u + \beta^2 /2)$$
$$= \lambda_0(t)\exp(\beta x(t) + \beta^2 kx(t)^2/2)$$
$$= \lambda_0(t)\exp(\beta_1 x(t) + \beta_2 x(t)^2)$$

where $\beta_1 = \beta$ and $\beta_2 = \beta^2 k/2$.

Therefore, in the situation where the standard deviation is proportional to the mean (constant coefficient of variation) risk would again be overestimated in one of two ways. If only the linear term in $x(t)$ is fit, the resultant coefficient would necessarily be greater than $\beta$ due to the positive effect of the term $\beta^2 x(t)^2/2$. If, however, the linear and quadratic terms in $x(t)$, are fit relative risk would be overestimated by the factor $\exp(\beta^2 kx(t)^2/2)$.

Of the three cases considered, only Case 1 (constant variance) results in an unbiased estimated of $\beta$ when the true risk function is log-linear and errors follow a Normal distribution. This result will prove to be important in the subsequent examination of the power function risk model.
4.3.2. Alternative Risk Functions

The discussion in section 4.3.1. assumed that the correct model in \( z(t) \) was \( \exp(\beta z(t)) \). It is of interest to consider alternative risk functions. If the true risk function is of the linear form \( R(t;z(t)) = 1 + \beta z(t) \) the hazard can be written:

\[
\lambda(t;x(t)) = \lambda_0(t) E[(1 + \beta z(t)) | x(t)].
\]

If \( E(z|x) = x \) the result is:

\[
\lambda(t;x(t)) = \lambda_0(t)(1 + \beta E[z(t)|x(t)])
\]

\[
= \lambda_0(t)(1 + \beta x(t)).
\]

Therefore, the linear risk function would be correctly estimated even in the presence of covariate errors as long as \( E(z|x) = x \). Cochran (1968) noted a similar situation for unbiased estimation in linear regression when the conditional expectation of the true independent variable was equal to the measured value. He referred to this situation as the Berkson Case.

Now consider a more general risk function which includes a quadratic term such that:

\[
\lambda(t;x) = \lambda_0(t) E[(1 + \beta_1 z + \beta_2 z^2 | x)]
\]

\[
= \lambda_0(t)(1 + \beta_1 E[z|x] + \beta_2 E[z^2|x])
\]

\[
= \lambda_0(t)[1 + \beta_1 E(z|x) + \beta_2 \text{var}(z|x) + \beta_2 E(z|x)^2]
\]

The three cases examined earlier are now considered.

Case 1: \( \text{var}(z|x) = k > 0 \)

\[
\lambda(t;x) = \lambda_0(t)[1 + \beta_1 x + \beta_2 k + \beta_2 x^2]
\]

\[
= \lambda_0(t)[1 + \beta_2 k][1 + \beta_1/(1 + \beta_2 k)x + \beta_2/(1 + \beta_2 k)x^2]
\]

\[
= \lambda_0(t)[1 + \beta_1 x + \beta_2 x^2]
\]

where \( \beta_1^* = \beta_1/(1 + \beta_2 k) \) and \( \beta_2^* = \beta_2/(1 + \beta_2 k) \)
Therefore, if \( \beta_2 > 0 \) the true relative risk coefficients \( \beta_1 \) and \( \beta_2 \) would be strictly underestimated. If \( \beta_2 < 0 \) the relative risk could be overestimated or underestimated depending on the relative magnitudes of \( \beta_1 \), \( \beta_2 \) and \( k \).

Case 2: \( \text{var}(z|x) = kx, \ k > 0 \).

\[
\lambda(t;x) = \lambda_0(t)[1+\beta_1 x \beta_2 k x + \beta_2 x^2]
\]

\[
= \lambda_0(t)[1+\beta_1 x + \beta_2 x^2]
\]

where \( \beta_1^* = \beta_1 + \beta_2 k \)

Therefore, if \( \beta_2 > 0 \) relative risk would be overestimated, while if \( \beta_2 < 0 \) the opposite would be true.

Case 3: \( \text{var}(z|x) = kx^2, \ k > 0 \)

\[
\lambda(t;x) = \lambda_0(t)[1+\beta_1 x + \beta_2 k x^2 + \beta_2 x^2]
\]

\[
= \lambda_0(t)[1+\beta_1 x + \beta_2 x^2]
\]

where \( \beta_2^* = \beta_2 k + \beta_2 \).

Therefore, as in Case 2 relative risk would be overestimated when \( \beta_2 > 0 \) and underestimated when \( \beta_2 < 0 \).

4.3.3. Effect of Right-skewed Error Distributions

Up to this point the effect of a symmetric error distribution (Normal) upon the log-linear risk function has been examined along with the effect upon linear and quadratic risk functions without specifying the form of the error distribution. Since in many practical situations the error distribution is right-skewed, it is of interest to examine the effect of such distributions upon relative risk estimates.
When the "true" risk function is log-linear, it is necessary to choose an error distribution with a closed-form specification of its moment-generating function in order to evaluate \( \mathbb{E}[\exp(bz) | x] \). The Gamma distribution is flexible in shape and is right-skewed when the shape parameter \( r > 1 \). For \( z, r, \lambda > 0 \), the density function is of the form:

\[
f(z) = \lambda^r / r! z^{r-1} \exp(-z\lambda).
\]

\( \mathbb{E}(z) = r/\lambda, \quad \text{Var}(z) = r/\lambda^2 = \frac{1}{\lambda} \mathbb{E}(z). \)

The moment generating function is:

\( \mathbb{E}(\exp(tz)) = (\lambda/(\lambda-t))^r. \)

The Gamma distribution has the property that the variance is proportional to the mean. This is equivalent to Case 2 considered in Section 4.3.2. which can be evaluated as:

\[
\mathbb{E}[\lambda_0(t)\exp(bz) | x] = \lambda_0(t)\mathbb{E}[\exp(bz) | x]
= \lambda_0(t)\left(\frac{\lambda}{\lambda - b}\right)^r,
\]

for \( b < \lambda \). Again, assume \( \mathbb{E}(z | x) = x = r/\lambda \), which implies \( r = \lambda x \). The restriction that \( b < \lambda \) implies that \( e^{bx} < e^{\lambda x} = e^r \). Since \( e^r \) may be less than 3.0 for some \( r > 1 \), this model of measurement errors may only be appropriate for situations when the relative risk is likely to be small.

When the restricted Gamma distribution is an appropriate error model the expectation can be written:

\[
\lambda_0(t)\mathbb{E}(\exp(bz) | x) = \lambda_0(t)(\lambda/(\lambda-b))^\lambda x
= \lambda_0(t)\exp[\lambda ln(\lambda/(\lambda-b))]x
= \lambda_0(t)\exp(b^\lambda x),
\]
where \( \beta = \ln(\lambda/(\lambda-\beta)) \). It can easily be shown that \( \beta = \ln(\lambda/(\lambda-\beta)) > \beta \) since for all \( \beta > 0, \lambda > \beta, \lambda/(\lambda-\beta) > \exp(\beta/\lambda) \). Therefore, ignoring right-skewed errors following some form of Gamma distribution will lead to an overestimation of the true relative risk.

Another possibility is a log-normal distribution of covariate errors. This distribution has no closed-form moment-generating function, so it is difficult to evaluate its effect upon a log-linear risk function. However, if the true risk function is of the form \( \exp(\beta \ln z) = z^\beta \) as indicated in Chapter II for this study, the effect of a log-normal distribution of individual exposure errors about the measured values, \( x \) may be evaluated. This may be written as:

\[
E[\lambda_0(t)z^\beta | x] = \lambda_0(t) \int_0^\infty z^\beta \left( \frac{1}{\sqrt{2\pi} \sigma z} \exp \left( \frac{\ln z - \mu)^2}{2\sigma^2} \right) \right) dz.
\]

Then substituting \( y = \ln z, z = \exp(y) \), and \( dy = dz/z \) yields:

\[
E[\lambda_0(t)z^\beta | x] = E[\lambda_0(t)\exp(\beta y) | x] = \lambda_0(t) \int_{-\infty}^\infty \exp(\beta y) \frac{1}{\sqrt{2\pi} \sigma} \exp \left( \frac{(y-\mu)^2}{2\sigma^2} \right) dy
\]

which can be recognized as the moment generating function for a normal distribution. Therefore, as would be expected, if the covariate errors are lognormal and true risk function is \( \exp(\beta \ln z) \) the situation reduces to that considered in section 4.3.1. Specifically, this is an exponential function of the logarithms of the covariates where the logarithmic errors of the measured covariates are normally distributed with mean = \( \ln x \) and constant variance, \( \sigma^2 \). This is equivalent to Prentice's assumption on the log scale, i.e., \( E(\ln z | \ln x) = \ln x \). This implies that the measured value \( x \) is assumed to be the geometric mean.
of the distribution of true individual exposures $z$ within any given mine and year. The variance of the logarithms of the covariates is assumed to be constant since the usual assumption with lognormal data is a constant coefficient of variation, i.e.

$$CV = \sqrt{\exp(\sigma^2) - 1}$$

Therefore, in this situation the procedure reduces to Case 1 in section 4.3.1. and $\beta$ would be correctly estimated if the risk function $\exp(\beta \ln x) = x^\beta$ is fitted to the measured covariate $x$.

4.4. Estimation of Error in Exposure Determinations

Since the individual cumulative exposure assessments used in this risk assessment are obviously subject to error, the magnitude and form of these errors must be determined. Specifically the following must be addressed:

1) the distributional form of the errors
2) the magnitude of the variance of this distribution
3) whether the distribution or its parameters changed over time

and 4) whether the distribution or its parameters differed according to the method of exposure assessment.

As mentioned in Chapter I, since every mine was not sampled for levels of radon daughters in every calendar year, the exposure assessment procedure consisted of four distinct methods. According to
Lundin, et al. (1971) the four methods (in reliability order) were:

1) actual measurements
2) interpolation or extrapolation in time
3) geographic area estimation
4) estimates prior to 1950 based upon knowledge of ore bodies, ventilation practices, and earliest measurements.

These methods of exposure determination will subsequently be called Methods 1, 2, 3, and 4. In assessing the error associated with individual exposure determinations we must first consider the error in precision introduced by each of the four methods.

**Method 1**

Table 4.1 provides a frequency count of white miners working underground from 1950-68 and the mean number of samples taken in each mine visited in those years. The Kusnetz procedure for measuring radon daughters was most often used during the period of study (Johnson and Schiager, 1981). This is an area monitoring method based on alpha counts collected on a filter/pump apparatus. The resulting data was generally thought to be of good quality (Lundin, et al., 1971). Data from mines in which five or more measurements were taken in a given year was analyzed. These data apparently followed a lognormal distribution with little change over the period 1951-1968. Prior to 1960 samples were taken largely by the USPHS, while post-1960 sampling was conducted by state mine inspectors. Therefore, data was separated into 1951-1960 and 1960-68 periods and estimates of the coefficient of variation (CV) were made for each period. Results
indicated a slight but non-significant increase in CV's after 1960 (106.6 percent versus 118.3 percent). Since the measurements were grab samples taken at different times within each mine, the total pooled CV=112.5 percent over the period 1951-1968 is assumed to include sampling errors, counting errors, and environmental fluctuations over time. This estimate agrees well with the CV of 110 percent found in an independent study of U.S. mines in the period 1973-79 when exposure levels were much lower. In other studies, however, an average CV of 30 percent was reported for area samples in Canadian mines (Makepeace and Stocker, 1979) while fluctuations of 20-30 percent around daily means were found for radon measurements in non-uranium Norwegian mines (Berteig and Stranden, 1981). Table 4.2 contains the error estimates for all four methods as characterized by CV's from a lognormal distribution.

**Method 2**

In order to assess the error in interpolating for gaps in sampling of one to three years, a simulation procedure was used. Mines having the longest periods of continuous annual measurements were identified. Then the even years' averages were omitted and the average of the two adjacent years was substituted. In this way it was possible to compare the observed annual average with the expected average had that year been missing. This strategy was repeated by imposing three year gaps in the data and again using the average of adjacent years to estimate the three intervening years.

The error variance attributable to Method 2 was then estimated by the usual calculation for the variance of logs when the expected
value is assumed to be known:

\[ \sigma^2 = \sum_{i} \left( \log\left( \frac{O_i}{E_i} \right) \right)^2 \]

where \( O_i \) = actual measurements for intervening years;

\( E_i \) = interpolated values estimated by average of adjacent years.

The resulting CV was 120.8 percent for one year interpolation and 137.3 percent for three year interpolation. Since these results were not significantly different they were pooled to yield a CV=131.9 percent.

Method 3

This method used annual mine averages in the same geographic locality to estimate radon daughter levels in mines for which Methods 1 and 2 could not be used. In order to assess the error associated with this method four of the uranium mining localities with the greatest number of annual measurements were selected. A simulation procedure similar to that used for Method 2 was employed. Annual averages for selected mines in these localities were omitted for one to four years. The averages for mines in the nearest district were substituted as the expected radon level if the annual average actually had been missing. The error variance was calculated in the same way as Method 2. The resulting CV was 148.6 percent for this method.

Method 4

No measurements were available in the period prior to 1950. Therefore, the estimates made using knowledge of ore bodies, ventilation and earliest known measurements in these mines could not
be verified. Since these estimates comprised less than 6 percent of the 34,120 annual averages used in exposure assessment, their impact was minimal. However, since the error for this method was probably the greatest of the four methods used, the overall CV for Method 4 was estimated to be 25 percent greater than that for Method 3, i.e., CV=186 percent.

Table 4.2. shows the number of annual averages for each of the four methods. Actual measurements comprised only about 10 percent of the data. In order to obtain an overall estimate of the relative error, a weighted average of the CV's for each method was calculated with weights based on the number of determinations for each method. The resulting overall CV=137 percent.

The error associated with each miner's cumulative exposure can then be calculated using our estimate of the error in each radon daughter level (WL). The total cumulative exposure (WLM) for each miner k is obtained from:

\[ \text{WLM}_k = \sum_{i,j} (\text{WL}_{ij})(\text{UGMON}_{ijk}) \]

where \( \text{WL}_{ij} \) is the estimated exposure for mine i in year j and \( \text{UGMON}_{ij} \) is the number of months spent underground in mine i during year j. The variance of WLM assuming independence of \( \text{WL}_{ij} \) is then:

\[ \text{Var}(\text{WLM}_k) = \sum_{i,j} (\text{UGMON}_{ijk})^2 \text{var}(\text{WL}_{ij}) \]

\[ = \sum_{i,j} (\text{UGMON}_{ijk})^2 (\text{CV})^2 (\text{WL}_{ij})^2 \]
where CV is the coefficient of variation for the estimated exposure \( WL_{ij} \).

If we substitute our estimate of the overall CV=137 percent, or 1.37, and use total cumulative exposure divided by total months underground (WLM/TOTMON) as an estimate of \( WL_{ij} \) for each individual miner, the average CV for cumulative exposure (WLM) is 0.97 or a relative standard deviation of 97 percent of the total WLM for each miner. Since radon daughter measurements were taken in different areas of each mine and often at different times of the day or week, we will assume that the variance in these measurements reflects the variance in exposure levels among individual miners, i.e.,

\[
\text{Var}(WL_{ij}) = \sigma_{ijk}^2
\]

where \( \sigma_{ijk}^2 \) = variance in exposure measurement for miner k in mine i and year j.

4.5. **Effect of Estimated Error in Exposure Measurements Upon Relative Risk Estimates in the Cox Model**

4.5.1. **Underlying Assumptions**

There are two conditions that must hold in order for the conditional expectation of the risk function as given in Sections 4.2. and 4.3. to be valid. First, the conditional expectation \( E(z|x) \) must be adequately represented by the measured value \( x \) so that \( E(z|x) = x \) is a valid statement. This is equivalent to assuming that the annual exposure level to radon daughters in a given mine and year is on
average equal to its measured (or assigned) value \( x \). Second, the variability of individual cumulative exposures about the measured value \( x \) must be accurately estimated by the variability in individual short term grab samples taken at different times and locations within each mine.

The situation is best formulated as a components of variance problem. The variance of interest, \( \sigma^2 \), is the variance in individual miners' exposures about the true annual exposure level for any mine and year. The total variance for each miner is therefore the sum of two different components such that:

\[
\sigma^2 = \sigma_1^2 + \sigma_2^2
\]

where \( \sigma_1^2 \) = variance of the estimated annual exposure level \( x \) about the true annual level \( z \)

and \( \sigma_2^2 \) = variance of individual miners' exposure about the estimated annual exposure level \( x \) for a given mine and year.

Since we cannot estimate each component separately, we assume that \( \sigma_1^2 \) is negligible when compared with \( \sigma_2^2 \). If this assumption is true the major contribution to the error in the covariate representing radon daughter exposure is the variability of individual miner exposures about the annual exposure level for any mine and year. A paper by Piechowski, et al. (1981) tends to support this assumption. They examined the relationship between radon measurements from area samplers and personal monitors in a French mine. They found that the personal samples followed a log-normal distribution with a
coefficient of variation as much as three times greater than that of the long-term area samples.

4.5.2. Effect of Errors in Radon Daughter Exposures on Log-linear Risk Function With Symmetric Error Distribution

In order to assess the effect of errors in radon daughter exposure assignments upon relative risk estimates the "true" form of the risk function must be assumed. For purposes of illustration the log-linear form is initially assumed even though it is not the best fit to this data. In this case the risk function is:

$$RR = \exp(\beta z)$$

for a miner with actual cumulative exposure $z$ compared to a non-exposed miner of the same age and smoking status.

If the distribution of the true exposure $z$ given assigned exposure $x$ is assumed to be:

$$f(z|x) \sim \text{Normal} \left(x, \sigma_x^2\right)$$

where $\sigma_x^2 = (CV)^2 x^2 = (0.97)^2 x^2 = 0.94 x^2$, we can estimate $\beta$ for the true exposure $z$. This is done by fitting a risk function of the form: $\exp(\beta x + (0.94/2)\beta x^2)$ which is the expected value $E(\exp(\beta z)|x)$ as demonstrated for Case 3 in Section 4.3.1 when the standard deviation is proportional to the mean.

The estimated true $\beta$ and its standard error are given in Table 4.3. Note that the first line labelled "CV=0.0" represents the estimated $\beta$ when errors are ignored. The magnitude of $\beta$ was reduced by over 50 percent (0.321 down to 0.159) when taking error of exposure
measurements into account. In order to assess the sensitivity of $b$ to the degree of error in exposure measurement, two additional estimates were made corresponding to CV's of 0.50 and 1.50. The results are given in Table 4.3 and Figure 4.1. It is apparent that the ratio of $b$ to its standard error is nearly constant as noted by Prentice (1982) when the error distribution is normal.

Although in Chapter II the log-linear risk function was not found to produce the best fit to this data, an important point has been demonstrated. The log-linear risk function used in most applications of the Cox model appears to be sensitive to errors in covariate measurements. The most striking result of this analysis is that relative risk is overestimated under these conditions when errors in covariates are ignored. This is in direct contrast to the popular notion that errors in exposure determination bias relative risk estimates toward the null. When the magnitude of measurement errors increases with exposure level, there is a similarity to differential misclassification. This is due to the fact that the magnitude of errors in an unexposed or low-exposed group would be lower than errors associated with higher exposed groups. As mentioned earlier, past research (Keys and Kihlburg, 1963) has shown that differential misclassification does not always result in underestimation of relative risk.

It has been NIOSH experience that industrial hygiene data from personal monitors within designated job areas often produce CV's exceeding 0.50. Even a CV of this magnitude would result in an overestimate of almost 40 percent from the true coefficient
(0.321/0.231) when ignoring the error in the covariate. This would be especially important when attempting to assess the relative risk for highly exposed persons.

The reason for overestimation of relative risk when ignoring covariate errors is due to the shape of the risk function and the error distribution. The exponential risk function (for \( \beta > 0 \)) increases more rapidly to the right of a given point than it decreases in an equal interval to the left. The expected value of such a function is simply the probability weighted average over the range of the function. In this case the probability density is symmetric so that when it is applied to an accelerating function like the exponential, the intervals to the right of a given point \( x \) have a disproportionately greater effect upon the weighted average. Thus, a symmetric distribution of errors when the true risk function is log-linear causes an overestimation of \( \beta \) when the errors are ignored. The problem would appear to worsen when the error distribution is actually right-skewed and the true risk function is log-linear. For some risk functions, however, a right-skewed error distribution is not a serious problem as is shown in the next section.

4.5.3. Effect of Exposure Assignment Errors on the Model of Interest

In Chapter III the power function model \( z^\beta \) was found to fit the data better than the log-linear model. Since \( \beta < 1 \) the risk function is convex. Based upon the argument at the end of the last section, such a model would be inherently less sensitive to covariate error. Indeed, in Section 4.3.3 it was shown that if the true risk
function were of this form and the exposure errors were lognormal with constant CV and median equal to the measured value x, β would be correctly estimated when ignoring the exposure measurement errors.

Although it is impossible to know whether the true risk function is of the form $z^β$, this model provided a reasonably good fit to the data. Likewise, it is not obvious that errors in individual exposure assignments are lognormal, but previous experience with similar data and the findings of Piechowski, et al. (1981) suggest that this is a reasonable assumption. It is probable, therefore, that relative risk estimates using the power function model are fairly insensitive to exposure measurement error in this data.

It should be noted that all of the development in this Chapter dealt with errors in exposure measurement. The actual dose delivered to lung tissues is a matter of much controversy. Dosimetry is a function of respiration rate, particle size, deposition and retention patterns, and equilibrium conditions of radon gas and radon daughters. It is beyond the scope of this research to deal with the relationship between exposure and dose.
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Figure 4.1

After correction for error in exposure measurements

Log-linear relative risk functions
CHAPTER V

SUMMARY AND SUGGESTIONS FOR FURTHER RESEARCH

5.1 Summary

5.1.1 Model Development

The primary goal of this research was to develop a model for quantitative risk assessment of lung cancer mortality due to exposure to radon daughters. The secondary goal was to determine the inter-relationships between radon exposure and various others factors in the etiology of lung cancer. The following is a summary of findings relative to these objectives.

All models considered in this study were in the family of proportional hazards models. Various types of these models were tried and the one providing the best fit in the maximum likelihood sense was a power function model of the form:

$$\lambda(t; z) = \lambda_0(t)z^8$$

The relative risk of a miner with exposure $z_1$, compared to a miner of the same age and smoking status with background exposure $z_0$ is:

$$RR = (z_1/z_0)^8.$$  

Using this model required augmenting each miner's cumulative exposure
by 0.2 WLM/year of age which is an estimate from independent studies of radon daughter exposure in homes. While the coefficient $\alpha$ was rather insensitive to small changes in the background rate (0.1 to 0.4 WLM/year), the risk estimates relative to an unexposed miner are changed by roughly $(z'_0/z_0)^8$ when using a background of $z'_0$ rather than $z_0$.

5.1.2 Other Factors Related to Relative Risk of Lung Cancer

A number of other factors were found to be important in the etiology of lung cancer among the U.S. uranium miners. Smoking showed a strong effect in this study with no interaction on the multiplicative scale. That is, the relative risk for a highly exposed miner who smokes compared to a low exposed, non-smoker is simply the product of the relative risks for high exposure and smoking. Cumulative smoking (pack-years) was a better index than smoking rate.

Exposure rate was found to be a statistically significant factor, with low exposures for long periods of time being, more hazardous than the equivalent amount obtained in a short period of time. This effect was not initially detected when using total years employed in underground uranium mining as the denominator. However, when the actual time spent underground was used, the effect was highly significant. This is also confirmed by the convex nature of the dose-response curve which indicates that lower amounts of radon daughters are more effective per unit of WLM than higher amounts. A number of previous studies of the U.S. miners failed to find such an
effect. One reason may have been the use of total duration of employment in the mines (including gaps) as the denominator in rate calculations. Another possibility is that different analytical methods were used in previous analyses, specifically, modified life table analysis and conditional logistic regression on case-control data.

5.1.3 Temporal Factors and the Multistage Model

A number of temporal factors also figured prominently in assessing an individual's risk in this study. Age at first employment was a statistically significant covariate with a positive coefficient. This implies that those miners first employed at later ages are at greater risk of lung cancer than those first employed at earlier ages, all else (including cumulative exposure) being equal. This is in contrast to A-bomb studies which show a constant relative risk as a function of age at exposure (Day, 1984). However, there are fundamental differences in exposure since A-bomb exposure was primarily gamma radiation received at one period in time whereas uranium miners are exposed primarily to alpha radiation over a prolonged period.

Time since last exposure (used as a time-dependent covariate) was also a significant factor in assessing relative risk. Unlike age at first exposure, this factor produced a negative coefficient. This implies that relative risk declines after cessation of exposure. This effect together with the positive influence of age at first exposure imply that radon daughter exposure acts at late stages of a multistage
carcinogenesis model. In contrast, the analysis of age at start of smoking and time since cessation of smoking implies that cigarette smoking acts at an earlier stage than radon daughter exposure, probably an intermediate one. This contradicts the hypothesis of Archer (1985) that exposure to radon daughters is an initiator while smoking is a promoter of lung cancer. Day (1984) argues, however, that A-bomb data and studies of ankylosing spondylitis seem to support the late stage activities of radiation exposure. Fry, et al. (1982) in a review of radiation carcinogenesis also finds evidence of the promoting action of nonionizing radiation. Since radon daughters are a form of ionizing radiation, our research would extend the findings of Day and Fry, et al., to high-energy alpha radiation.

5.1.4 Weighting Exposure

Most carcinogenesis studies now recognize the importance of lagging exposure. The question still being discussed is how long and in what manner. Three approaches were investigated: simple lagging for T years, lagging combined with partial linear weighting for an additional period of time, and weighting exposure using a distribution such as the lognormal.

For simple lagging, a 6-year lag of radon exposure provided the highest log-likelihood. This method, while widely used, is somewhat unsatisfying since it assumes that exposures suddenly change from totally ineffective to completely effective at one point in time. A more appealing method is lagging for a shorter period of time to remove
redundant exposure (during the tumour growth period) and a linear phase-in of exposure for a subsequent period of time. In our data a 4-year lag followed by a 6-year linear weighting from 4 to 10 years provided a fit that was about the same as a 6-year lag but biologically more plausible. The lognormal weighting function was discounted as a viable method for quantitative risk estimation since it produced relative risks far out of range of all other analyses.

Although some form of weighting exposure is generally required in cancer studies, it seems that it should be tied to prior knowledge or investigation of the stage at which the carcinogen acts. Therefore, short lags (4-6 years) are more appropriate for late stage carcinogens (e.g. radon daughters) while longer lags (10-15 years) may be more appropriate for early stage carcinogens. In fact, investigation of the fit of a model using various lags may aid in determining the stage at which the carcinogen is effective.

5.1.5 Effect of Errors in Exposure Measurement

Possibly the greatest impediment to a quantitative risk assessment are errors in exposure measurements. A considerable amount of work has been done concerning the effect of misclassification on risk estimation. Most of this work considered non-differential misclassification when exposure was dichotomized (i.e., equal sensitivity and specificity between comparison groups). In general, this form of error biases relative risk estimates toward the null. This seems to have led to a common misperception that errors in exposure determination always result in conservative results.
Little work has been done, however, regarding the effect of errors in continuous exposure measurements upon some form of the proportional hazards model. Specifically, the situation was considered where industrial hygiene area samples are used to characterize exposure levels in a job area (a mine, in this case) over a period of time. This level is then assigned to everyone working in that area during that time. Under this commonly occurring set of conditions, it can be shown that risk estimates depend upon the distribution of individual exposures about the measured value and upon the shape of the true dose-response curve. If one conditions on the distribution of the true individual exposures about the measured value, it is possible in many situations to derive an unbiased estimate of relative risk. The most interesting outcomes of this research are that relative risk is usually overestimated when using the standard exponential risk function in the Cox model assuming a Normal distribution of covariate errors which increase with exposure level. On the other hand, if the distribution of covariate errors is lognormal (which is probable in the U.S. uranium miners data) the effect on relative risk is negligible if the true risk function is a power function of the form $z^B$.

The end result of these analyses is a convex dose-response curve best expressed as cumulative exposure raised to a power of $0.74 \pm 0.07$. Smoking exerts a strong, but independent effect, best expressed as pack-years raised to the power of $0.39 \pm 0.07$. Other factors with a significant effect upon relative risk include exposure rate and age at first exposure and the effect modifiers birth decade and age at risk.
5.2 Suggestions for Further Research

Because the 1977 follow-up used in this analysis includes few lung cancer deaths at low exposures, risks relative to background exposure are somewhat unstable. The cohort is still being followed and application of these models to later follow-up may prove very beneficial in setting standards of exposure to radon daughters.

Several other areas of model development should also be addressed. The optimum number of controls to be matched to each case in a synthetic case-control approach to cohort studies is still questionable when the actual relative risk is likely to be large. This issue should be resolved. A generalized goodness-of-fit test for the proportional hazards model would be very useful, especially in determining the appropriate risk function. A procedure for estimation of the appropriate lag for carcinogenesis studies when using the proportional hazards model should be investigated. The empirical approach used in this analysis is often not feasible when computer time is an important cost factor.

An attempt has been made in this research to address the effect of errors in covariate measurement upon relative risk estimation. Situations were considered which were manifested in the U.S. uranium miners data. However, there are many other situations which still need to be examined. Specifically, the effect of errors in individual personal monitoring should be addressed. Increased awareness of the health effects of occupational exposures has made personal monitoring much more prevalent than just a decade ago. In
the future more data of this quality will be available for epidemiologic research. Methods for estimation of risk in the presence of error when actual measurements on each individual worker are available should be developed.
LIST OF REFERENCES


Kalbfleisch, J.D. (1974). Some Extensions and Applications of Cox's Regression and Life Model, Biometrics 30, 561-


APPENDIX A
EXAMPLE OF TIME-DEPENDENT BMDP2L PROCEDURE

The software used throughout the risk analyses in this study is a modification of the BMDP2L procedure "Survival Analysis with Covariates - Cox Models." This procedure was originally written to enable the user to perform survival analyses using the Cox proportional hazards model with survival time from entry into the study as the time dimension. The unique feature of this commercially available software is its ability to incorporate into the model covariates which change over the period of follow-up. This can be done either through the use of a FUNCTION paragraph in the control language, or for more complicated applications, a FORTRAN subroutine may be supplied by the user. Either of these two choices can be used to define values for the covariates at each failure time evaluated in the analysis.

When using survival time from entry into the cohort as the time dimension, the risk sets decrease monotonically as the ordered failure times increase. The modification to the software was necessary to permit the user to manipulate membership in each risk set when age at failure was used as the time dimension. Control of risk set membership is necessary since subjects may enter the cohort at different ages. Therefore, for a given failure time (age at death) a surviving subject may not have yet entered the cohort, and thereby would not be at risk of dying from the cause of interest. This situation causes the risk
sets to fluctuate in a non-monotone fashion as the ordered failure times are evaluated.

Membership in the risk set associated with each failure is controlled by using the LEVEL parameter in the FORTRAN subroutine which defines the time-dependent covariates for each subject. The FORTRAN subroutine is designated as P2LFUN. When the user sets the value of LEVEL=0 for any subject in the study, that subject is removed from consideration in the likelihood function at the particular failure time being evaluated.

The software was also modified to permit the user to consider alternatives to the usual log-linear risk function. The user may introduce any positive, differentiable risk function into the model through use of a second FORTRAN subroutine designated P2LRSK. When using this subroutine the user must define the risk function to be used and its first derivative. The risk function must be designated as RISK and the first derivative as DRDB. When using a user-supplied risk function, the analyst must also include the sentence RISK=USER. in the REGRESSION paragraph of the BMDP control language.

In order to illustrate the use of this software two examples are provided. The first demonstrates the use of the P2LFUN subroutine to define cumulative exposure as a time-dependent covariate called DOSE. The default option in this example is the log-linear risk function \( \exp(\beta_1 \cdot \text{DOSE} + \beta_2 \cdot \text{YRSTART}) \). YRSTART is used in these examples as a fixed covariate. The second example illustrates the use of the subroutine P2LRSK to define a linear risk function \( 1 + \beta_1 \cdot \text{DOSE} + \beta_2 \cdot \text{YRSTART} \). The reader should refer to the BMDP user's manual for a detailed description of all other BMDP statements used in
these examples. Both examples were run on subsets of the actual data for illustrative purposes and results should not be compared to those reported in Chapter II.

The following is a listing of the BMDP Control language necessary to execute the first example.

BMDP Instruction Language

/PROBLEM TITLE IS 'EXAMPLE NO. 1'.
/INPUT VARIABLES ARE 17.
/FORMAT FORMAT IS FREE.
/VAR NAMES ARE BIRTHYR,FLAG,YRSTART,TIME1,TIME2,TIME3,
 TIME4,TIME5,TIME6,TIME7,TIME8,TIME9,AGEDIED,IND,AGESTART.
/TRANSFORM IF (BIRTHYR LT 807) THEN BIRTHYR=1.
 IF (BIRTHYR GE 807) THEN BIRTHYR=2.
/FORM TIME IS AGEDIED.
/REGR "PASS2. MEANS. COVARIATE=YRSTART ADD=DOSE,
 AUX=TIME1,TIME2,TIME3,TIME4,TIME5,TIME6,TIME7,
 TIME8,TIME9,FLAG,TOTDOSE,AGEDIED,AGESTART,BIRTHYR.."

The variables designated TIME1, TIME2, ..., TIME9 are ages at which each miner accumulated certain fixed exposure levels which are arrayed in P2LFUN. These variables are used in P2LFUN to linearly interpolate the exposure accumulated at any failure time (age) being evaluated in the analysis. For this example birth year is divided into two strata. Membership in each strata is checked in the subroutine, and a subject not in the strata being analyzed is eliminated from consideration by setting LEVEL=0. The control variable PASS is set equal to the number of strata in order that two passes are made through the likelihood calculations, one for each stratum.
The following is a listing of the subroutine P2LFUN written to execute the first example.
The output from this example follows.

**INDEPENDENT VARIABLES**
3 YRSTART  1B DOSE

<table>
<thead>
<tr>
<th>ITERATION</th>
<th>LOG LIKELIHOOD</th>
<th>PARAMETER ESTIMATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-104.26694730</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>-105.05628114</td>
<td>0.035752</td>
</tr>
<tr>
<td>1</td>
<td>-101.51676285</td>
<td>0.017876</td>
</tr>
<tr>
<td>2</td>
<td>-101.30581810</td>
<td>0.030183</td>
</tr>
<tr>
<td>3</td>
<td>-101.30319300</td>
<td>0.031733</td>
</tr>
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<td>4</td>
<td>-101.30319246</td>
<td>0.031756</td>
</tr>
</tbody>
</table>

LOG LIKELIHOOD = -101.3032
GLOBAL CHI-SQUARE = 8.50  D.F. = 2  P-VALUE = 0.0143

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>COEFFICIENT</th>
<th>STANDARD ERROR</th>
<th>COEFF./S.E.</th>
<th>EXP(COEFF.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 YRSTART</td>
<td>0.0314</td>
<td>0.0222</td>
<td>1.4322</td>
<td>1.0323</td>
</tr>
<tr>
<td>1B DOSE</td>
<td>0.2739</td>
<td>0.0492</td>
<td>2.7607</td>
<td>1.3151</td>
</tr>
</tbody>
</table>

Statistical significance of covariates may be assessed by comparing the coefficient divided by its standard error to the appropriate standard normal value (based on asymptotic properties of this ratio).

The second example demonstrates the software necessary to fit a linear risk function to the data. The `BMDP` control statements are identical to those reported in the first example, with one exception. The user must alert the main program to expect a second subroutine by including the statement RISK=USER. in the REGRESSION paragraph. The subroutine `P2LFUN` will also be identical to that given for the first example. Immediately following the `P2LFUN` subroutine the user must supply a second subroutine called `P2LRSK`. 
The following is a listing of this subroutine for the second example.

```
RELEASE 2.0   P2LSK   DATE = 84102 18/26/11

SUBROUTINE P2LSK(RISK,DRDB,BETA,Z,NCOVAR)
DOUBLE PRECISION RISK,DRDB,BETA
DIMENSION DRDB(NCOVAR),BETA(NCOVAR),Z(NCOVAR)
RISK=0.0
C DEFINE OPTIONAL RISK FUNCTION: RISK=1+BETA1*Z1+BETA2*Z2
DD 5 J=1,NCOVAR
RISK=RISK+BETA(J)*Z(J)
5 CONTINUE
RISK=1.0*RISK
C CALCULATE DERIVATIVE OF RISK FUNCTION WITH RESPECT TO EACH BETA
DO 10 J=1,NCOVAR
DRDB(J)=Z(J)
10 CONTINUE
CONTINUE
RETURN
END
```

The first three statements are fixed for any use of P2LSK. They must be provided exactly as they are listed above. The remaining FORTRAN code may be tailored to the specific risk function desired by the user. Output from this example is listed below.

PAGE 5  BMDP2L EXAMPLE NO. 2

INDEPENDENT VARIABLES
3 YRSTART  18 DOSE

<table>
<thead>
<tr>
<th>ITERATION</th>
<th>LOG LIKELIHOOD</th>
<th>PARAMETER ESTIMATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>0.0</td>
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<tr>
<td>1</td>
<td>101.66003454</td>
<td>0.035752 0.502937</td>
</tr>
<tr>
<td>2</td>
<td>101.60751731</td>
<td>0.039034 0.534767</td>
</tr>
<tr>
<td>3</td>
<td>101.56567377</td>
<td>0.043017 0.583427</td>
</tr>
<tr>
<td>4</td>
<td>101.56055557</td>
<td>0.043488 0.580045</td>
</tr>
<tr>
<td>5</td>
<td>101.55816857</td>
<td>0.044227 0.588066</td>
</tr>
<tr>
<td>6</td>
<td>101.55755743</td>
<td>0.044469 0.588706</td>
</tr>
</tbody>
</table>

LOG LIKELIHOOD = 101.5676
GLOBAL CHI-SQUARE = 8.50  D.F. = 2  P-VALUE = 0.0143

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>COEFFICIENT</th>
<th>STANDARD ERROR</th>
<th>COEFF./S.E.</th>
<th>EXP(COEFF.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 YRSTART</td>
<td>0.0445</td>
<td>0.0276</td>
<td>1.56130</td>
<td>1.0455</td>
</tr>
<tr>
<td>18 DOSE</td>
<td>0.5687</td>
<td>0.5666</td>
<td>1.0354</td>
<td>1.0017</td>
</tr>
</tbody>
</table>