FINAL REPORT

TIME-RELATED FACTORS IN RADIATION-CANCER DOSE RESPONSE

Grant Number: R03 OH03343

August 5, 1997

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50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	PB98-130925

4. Title and Subtitle
Time-Related Factors in Radiation-Cancer Dose Response

5. Report Date
1997/08/05

6.

7. Author(s)
Wing, S. B., and D. B. Richardson

8. Performing Organization Rept. No.

9. Performing Organization Name and Address

10. Project/Task/Work Unit No.

11. Contract (C) or Grant(G) No.
(C)
(G)
R03-OH-03343

12. Sponsoring Organization Name and Address
Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, North Carolina

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words) The effects of low level, external exposure to ionizing radiation on the mortality of workers at Oak Ridge National Laboratory (ORNL) were investigated. The retrospective cohort study included 14,095 ORNL workers hired between 1943 and 1972 and followed through 1990. The focus on the analysis was on time related factors which influenced the association between all cancer mortality rates and cumulative external radiation dose. The data indicated that the cumulative dose received after age 45 strongly predicted all cancer mortality among these workers under a range of lag assumptions, and provided estimates of similar magnitude for lung cancer mortality and mortality from cancers other than lung. The cumulative dose received at older ages was more strongly associated with subsequent cancer mortality than lifetime cumulative dose. The strong evidence of a dose response relationship and the substantial magnitude of this association suggest that by considering age at exposure a smaller, more relevant time period of exposure can be identified. The authors suggest that if the effects of low level radiation do indeed increase with age, then differences in radiosensitivity need to be incorporated into considerations of radiation protection, medical uses of radiation, and the implications of industrial and military applications of nuclear technologies.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms

NIOSH-Publication, NIOSH-Grant, Grant-Number-R03-OH-03343, End-Date-06-30-1997, Pulmonary-system-disorders, Lung-cancer, Humans, Radiation-exposure, Cancer-rates, Epidemiology, Age-factors, Risk-analysis, Nuclear-radiation, Ionizing-radiation, Occupational-exposure

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
		229
	22. Security Class (This Page)	22. Price

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LIST OF ABBREVIATIONS

AML -	Acute Myeloid Leukemia
AS -	Ankylosing Spondylitis
BEIR -	Biological Effects of Ionizing Radiation
CLL -	Chronic Lymphocytic Leukemia
DOE -	Department of Energy
d.f. -	Degrees of Freedom
ICD -	International Classification of Diseases
LET -	Linear Energy Transfer
LSS -	Life Span Study of Atomic Bomb Survivors
MDD -	Minimum Detectable Dose
MH -	Metropathia Haemorrhagica
mSv -	Milli-Sievert
NDI -	National Death Index
ORNL -	Oak Ridge National Laboratory
PSR -	Physicians for Social Responsibility
p-y -	Person-Year
se -	Standard Error
SMR -	Standardized Mortality Ratio
SPEERA -	Secretarial Panel for the Evaluation of Epidemiologic Research Activities
TB -	Tuberculosis
TLD -	Thermoluminescent dosimeter
WWII -	World War Two

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Preface

Previous analyses of workers at ORNL have focused on a cohort, first defined by Checkoway et al., of white males hired between 1943 and 1972. In this report we refer to this group as the *Checkoway cohort*. The Checkoway cohort was limited to white males, in part, because these workers had the most complete vital status follow-up and the largest radiation exposures. In this study we have expanded the study population to make it more representative of the workforce actually employed at ORNL. This report describes analyses of an *expanded cohort* which includes all workers hired at ORNL between 1943 and 1972 for whom data was adequately complete.

In order to evaluate the consequences of using an expanded cohort, we first examined associations between external ionizing radiation and cancer mortality among the Checkoway cohort, and subsequently examined these associations among the expanded cohort of workers. The outline of this report reflects this strategy. Chapter One presents our specific aims and an introductory literature review. Chapter Two presents cohort definitions for the Checkoway cohort and for the expanded cohort, as well as a discussion of the variables considered in these analyses. Chapter Three describes our analytical and statistical methods. We used a regression model previously developed for analyses of the Checkoway cohort; however, to conduct analyses using data for the expanded cohort, we had to develop a regression model which included several additional variables. Consequently, Chapter Four presents univariate analyses of the distribution of cancer deaths and person-time within the expanded cohort; and, Chapter Five describes the development of a baseline regression model for the expanded cohort.

A primary concern of these analyses was the influence of age at exposure, latency, and time-since-exposure on estimates of the association between radiation and cancer mortality. These analytical questions were first investigated among the Checkoway cohort, for whom data were most complete, and among whom we had least concern about heterogeneity in radiation-cancer associations. Chapter Six presents our investigation of the influence of time-related factors on the association between radiation and all cancer mortality among the Checkoway cohort. After establishing the time-related factors of primary interest, we examined these associations in the expanded cohort. Chapter Seven presents analyses of the effects of age at exposure and latency among the expanded cohort. Chapter Eight further investigates these associations in the expanded cohort, examining the association between external radiation and specific cancer and non-cancer causes of death, with an interest in outcomes that could suggest problems of confounding. Finally, Chapter Nine discusses our results, comparing findings between analyses of the Checkoway cohort and analyses of the expanded cohort, as well as comparing our findings to other reports on radiation health effects.

SIGNIFICANT FINDINGS

Cumulative dose received after age 45 strongly predicts all cancer mortality among these workers under a range of lag assumptions, and provides estimates of similar magnitude for lung cancer mortality and mortality from cancers other than lung. These analyses suggest that among workers at ORNL cumulative dose received at older ages was more strongly associated with subsequent cancer mortality than lifetime cumulative dose. The strong evidence of a dose response relationship, and the substantial magnitude of this association, suggest that by considering age at exposure we identified a smaller, more relevant time period of exposure.

USEFULNESS OF FINDINGS

An estimated six hundred thousand workers have been employed by the DOE and its predecessor organizations in the nuclear industry,[12] and many more people have been affected by environmental releases of radiation from nuclear facilities and by medical and occupational radiation sources. Epidemiologic research on low level radiation provides information to the public about the consequences of these exposures. Information about differences in sensitivity to radiation health effects needs to be coupled with more information about the sources of radiation exposure, in order to aid public evaluation of the risks created by nuclear technologies. These results raise important questions about the magnitude of estimates of radiation-cancer associations currently used for worker protection and environmental regulation, and support previous findings of evidence that adults' sensitivity to radiation increases with age. Data from DOE cohorts is important for evaluating these questions. The results of cohort studies of badge-monitored workers, with extremely complete vital status follow-up deserve particular attention. We have identified age at exposure as an important determinant of differences in the effects of radiation among workers at ORNL. If, as these results suggest, the effects of low level radiation increase with age, then differences in radiosensitivity need to be incorporated into considerations of radiation protection, medical uses of radiation, and the implications of our industrial and military applications of nuclear technologies.

ABSTRACT

This report examines the effects of low-level, external exposure to ionizing radiation on mortality among workers at Oak Ridge National Laboratory (ORNL). A retrospective cohort study examines 14,095 ORNL workers hired between 1943 and 1972 who were followed through 1990. Analyses focus on time-related factors influencing the association between all cancer mortality rates and cumulative external radiation dose. A limited number of analyses further considered all cause mortality, all causes except cancer, lung cancer, all cancers except lung, leukemia, ischemic heart disease, non-malignant respiratory disease, and external causes. The effects of external radiation dose were larger for doses received at older ages. Assuming a five year lag between exposure and death, a 4.39 % (se=1.36) increase in all cancer mortality was estimated per 10 mSv cumulative dose received after age 45. This association increased to 4.98 % (se=1.48) per 10 mSv under a ten year lag, and 7.31 % (se=2.24) per 10 mSv under a twenty year lag. Lung cancer mortality followed a similar pattern to all cancer mortality, while little evidence of association was observed between all non-cancer causes of death or leukemia and radiation.

Chapter One - Introduction And Literature Review

Introduction

For thousands of years the only exposures to ionizing radiation which people received were the emissions of the sun and soil. This has changed, however, over the last century, and particularly over the last fifty years, as technologies have developed around the promises and profits of ionizing radiation and the sources of exposure have multiplied.[1] Today, exposure to low level radiation is common for workers in many industries, for patients receiving medical and dental care, and for everyone exposed to the environmental releases from nuclear facilities, weapons detonations, and waste sites.[2-4] Consequently, while exposures from these new radiation technologies have occurred only recently, questions about their long-term effects are of broad public concern.[5]

One way to address questions about the long-term health effects of low level exposure to ionizing radiation has been to study workers in the nuclear industry, many of whom were hired during the early development of nuclear reactors and the United States' atomic weapons program.[3] Summarizing what has been learned from these occupational studies, the National Academy of Science's Committee on the Biological Effects of Ionizing Radiation noted that no study has found "results which differ significantly from the null."[3] Similarly, discussing the literature on occupational exposures to radiation, researchers for the International Agency for Research on Cancer concluded that "in most studies the confidence intervals of risk estimates were compatible with a range of possibilities, from negative effects to risks an order of magnitude greater than those on which current radiation protection recommendations are based."[6, 7] Such "null" findings were interpreted by the authors as consistent with findings from the Life Span Study (LSS) of atomic bomb survivors, which

estimate a 0.1% increase in all cancer mortality per 10 mSv dose.[7] The LSS has served, in this way, as an interpretative framework through which the results of other epidemiologic studies of populations exposed to ionizing radiation have been read.[8]

The history of research on low level radiation effects, however, is not constituted only by findings that converge at consensus; and, the statistical models which describe the waves of mortality moving out from the ground-zeros at Hiroshima and Nagasaki do not offer an overarching, or even adequate, summary of what has been reported about the effects of low level radiation on human health.[9-12] Rather, the literature on radiation health effects is marked with inconsistent findings and critical debate.[12-14] The work of Alice Stewart and George Kneale, for example, has repeatedly demonstrated differences in the effects of radiation depending on time-related factors, suggesting that low doses of radiation received at older ages and under long latency assumptions, may be associated with substantial increases in cancer mortality.[10, 15-18] Other researchers, reporting on occupational studies of exposure to ionizing radiation, have also reported associations more than ten-fold larger than the estimates derived from the study of A-bomb survivors.[19-22]

It has been suggested that studies which diverge from the findings of the LSS are likely to represent random error, problems of bias and confounding, and the proclivity of journals to print studies with positive rather than null findings.[3, 23] Some have argued that interpretation of research findings on the effects of low level radiation should give primacy to the results of the LSS, relegating findings that diverge from these estimates to the domain of outliers and statistical aberrations.[3, 23, 24] Others contend that the LSS also suffers the problems of biases, that the literature on radiation health effects contains substantial inconsistencies, and that we should continue to look for the threads of continuity which stitch together the entire body of this research.[9, 13, 14]

Establishing the historical ground upon which this research moves is important to the introduction of this dissertation, since our formulation of what is not understood about the effects of radiation exposure, and what appears promising for future research, arises from the overview of past research that we construct.[25] Similarly, the interpretation that we give to study findings is influenced by our understanding of what has been established by past researchers.[26]

A critical evaluation of questions about the effects of low level radiation is important to the public's health. Over six hundred thousand Department of Energy (DOE) workers have been occupationally exposed to low level radiation;[12] the number of others occupationally, medically, and environmentally exposed to ionizing radiation is much larger.[2] Currently, the LSS provides the basis for most radiation risk estimates and radiation protection standards limiting these exposures.[27] The findings of this dissertation, however, along with a substantial body of previous work,[14, 16, 28-31] challenge the conclusions currently drawn from the LSS, in particular the conclusion that radiation sensitivity decreases with older age.[27] These results need further attention, given the importance of such differences to our understanding of the health effects from the public's exposures to the wide range of medical, environmental and occupational irradiation.

Specific Aims

Compared to other workers in the nuclear industry, workers employed at Oak Ridge National Laboratory (ORNL) have a long history of vital status follow-up and particularly detailed information about external radiation exposure, especially for exposures received in the early years of operation of the nuclear industry. Consequently, this cohort provides some of the best data available on occupational radiation exposure. Previous studies have focused on the white males employed at ORNL. The goal of this study was to examine the association between external ionizing radiation and cancer mortality in an expanded ORNL cohort, while considering time-related factors which may affect estimates of the dose-response relationship as well as help to explain changes in these associations over periods of follow-up.[19, 32] To do this, recently developed methods for analysis of time-related factors in cohort studies were applied.

We examine an expanded cohort of workers at ORNL, including the most recent data on vital status follow-up, and incorporating records that allowed us to consider workers with previous employment at other DOE facilities. Analyses consider differences in the effects of radiation depending on lag assumptions, time since exposure, and the age at which exposure occurred. Interpretation of these findings addressed concerns about time-related patterns of confounding, and the influence of modeling assumptions on these estimates. In order to achieve our analytical goals, we addressed the following specific aims:

1. Examine the association between external radiation dose and total cancer mortality:

    a. Considering a range of standard lag assumptions.

    b. Evaluating the effects of expanding the cohort definition to include women, workers of all races, and those employed at other facilities.

c. Evaluating the sensitivity of these estimates to assumptions about the form (additive relative risk versus multiplicative relative risk) of our regression models.

2. Investigate differences in the effects of exposures received at different ages.

a. Evaluating the separate effects of exposures received at younger and older ages.

b. Considering the consistency of these effects between periods of hire and follow-up.

c. Considering differences in the effects of age at exposure under different lag assumptions.

3. Investigate critical time periods of exposure using induction time analyses. These analyses examine exposure time-windows that simultaneously consider lag and time-since-exposure. We considered time-windows of exposure as an alternative to age at exposure.

Background And Literature Review

The radiation exposure received by workers at ORNL is primarily due to gamma rays, a form of high energy electromagnetic radiation which is emitted as unstable nuclei undergo radioactive decay. Gamma radiation carries a tremendous amount of energy. As gamma radiation passes through the body, however, very little of that energy is lost to the surrounding environment.[33] Nonetheless, the energy which is expended is sufficient to remove an electron from an atom, break molecules apart, and, by what is known as the Compton effect, create cascades of ionized molecules.[3, 4] Because the energy of gamma radiation is delivered in discrete quanta, known as photons, even the lowest levels of exposure set these disruptive, ionizing, processes in motion.[34]

When ionizing radiation penetrates the human body, one type of molecule which can be damaged is DNA.[35, 36] This damage to chromosomes may occur directly from the interaction of the genetic material with ionizing radiation, or as an indirect consequence of the formation of free radicals by ionizing radiation, which then react with chromosomes or other cellular material involved in transcription or repair processes of the chromosomes.[34] The damage to DNA may consist of a single point mutation, which is a change in a single nucleotide base-pair. Alternately, both strands of a chromosome may be broken, causing structural changes to the DNA, such as the deletion or translocation of sections of chromosomal material, or the creation of dicentrics, or ring chromosomes.[33, 37] Evidence of deletions, translocations, dicentrics, and ring chromosomes following exposure to ionizing radiation have been reported in laboratory experiments and among people with occupational, medical, and environmental exposures to radiation.[3, 38-40]

Mutations and chromosomal abnormalities are widely believed to be important to the development of cancer. Chromosome abnormalities, while of low occurrence in the general population, are found almost universally in cancer cells. Furthermore, diseases such as ataxia telangiectasia, which predispose a person to chromosome breakage and

rearrangement, also predispose them to subsequent cancer mortality.[3, 41] Specific chromosome abnormalities have been associated with certain types of cancer, suggesting their role in the cancer's origin. For example, chronic myelocytic leukemia and Burkitt lymphoma have both been associated with specific translocations between chromosomes; and, small-cell carcinoma of the lung, renal carcinoma, neuroblastoma, Wilms' tumors, retinoblastoma, and osteosarcoma have been associated with specific deletions of chromosomal material.[3, 41]

The effects of low level radiation exposure on the occurrence of chromosomal aberrations may increase for doses received at older adult ages, perhaps because of the declining ability of cells' repair mechanisms at older ages.[42, 43] Among infants, children, and young adults receiving medical irradiation, the yield of chromosomal aberrations does not appear to vary with age at exposure.[44, 45] In studies of shipyard workers, however, radiation doses received after age 40 were associated with larger increases in the occurrence of dicentrics than doses received at younger ages.[46, 47] Studies of workers at the Rocky Flats nuclear facility also found that the association between plutonium body burden and chromosomal aberrations was greater among workers exposed after age 40 than among workers exposed at younger ages.[48-50]

However, age differences in the association between radiation and cancer mortality may be expected for reasons other than the physical processes associated with radiation-induced chromosomal damage and its subsequent repair. Stewart and others have argued that the relative effect of radiation may be expected to increase for exposures received at older age, since sensitivity to the effects of most exposures increases as a person ages and the body's repair and immune system deteriorates.[2, 16, 51] Furthermore, cancer development is likely to be mediated by many exposures during an individual's life.[52] At older age, a person may be more likely to have received previous exposures which initiate carcinogenic processes.[53] The belief that

cancer development is multi-stage process is supported by the evidence of long latency periods between exposures and subsequent cancer, the effects of age on cancer incidence, and evidence that different exposures may act as initiators or promoters of cancer.[54] Theoretical models of such multistage processes suggest that the effect of an exposure depends on the age at which exposure occurs.[55] Under a multistage model of cancer, in order for cancer to occur a cell must pass through several sequential changes.[56] A carcinogen may act as an initiator, at an early stage of carcinogenesis, and/or act as a promoter, at a later stage in the development of cancer.[57] Since the age at which an exposure occurs is related to the probability of a cell having undergone the necessary transitions preceding the stage upon which the exposure acts, age may modify an exposure's effect.[58]

Epidemiologic studies of occupational exposure to external ionizing radiation

The importance of considering differences in the relative effect of radiation doses received at different ages was raised by Mancuso, Stewart, and Kneale, in their early reports on cancer mortality among DOE workers at the Hanford facility.[59, 60] An analysis of radiation-cancer associations among workers at the Hanford facility compared accumulated doses among Hanford workers who died from cancer to the doses accumulated among workers who died from non-cancer causes. Higher mean cumulative doses were reported among workers who died from cancer than among workers who died from other causes. The authors noted that "data from the Hanford study have shown that sensitivity to the cancer-induction effects of radiation is at a low ebb between 25 and 45 yr of age."[59]

Their findings were followed by analyses by other researchers which reported lower cancer mortality among workers at Hanford than among the general population, and little evidence of dose response relationships between cumulative radiation and cancer mortality, with the exception of positive associations with multiple myeloma and carcinoma of the pancreas.[61-63] An early criticism of Stewart and Kneale's work

was their choice of analytical methods. Kneale subsequently presented a comparison of the methods used their early analyses with methods based on Standardized Mortality Ratios (SMRs),[64] and presented further analyses using Cox regression methods.[18, 60]

Reporting on vital status follow-up of the Hanford cohort through 1986, Stewart and Kneale reported positive associations between radiation and cancer mortality, with exposures received after age 50 being most important to this relationship.[18] Gilbert et al., in contrast, reported negative associations between cumulative radiation dose and leukemia mortality and all cancer mortality except leukemia.[65]

Stewart and Kneale have argued that attention to time-related factors, such as age at exposure, year of exposure, and latency, are fundamental to explaining the differences in results between their research and that of Gilbert et al.[66, 67] While Gilbert et al. focused on the association between cancer mortality and cumulative radiation dose under a ten year latency assumption, Stewart and Kneale evaluated the effects of numerous time-related factors. Recognizing the complexity of analyses which simultaneously evaluate several time-related factors, Stewart and Kneale later published analyses which focused on the effects of age at exposure under a ten year lag assumption.[16]

Critics have cautioned that Stewart and Kneale, by examining long latency assumptions and doses received only at older age, restrict dose response analyses to very small ranges of dose accrued over a short time interval.[68] Stewart and Kneale, however, have presented tables of observed and expected deaths by dose which allow assessment of the dose distribution upon which estimates were derived, and have presented comparisons of dose response associations for exposures received at younger and older ages.[16, 69] Stewart and Kneale have also reported analyses which, by comparing dose response associations for lung cancer and other respiratory

diseases, suggest that confounding by cigarette smoking is unlikely to account for the radiation-cancer dose response relationships they observed at Hanford.[70]

Researchers have combined data for workers from ORNL, Hanford, as well as at the DOE's Rocky Flats facility in order to conduct 'pooled' analyses.[71, 72] Such pooled analyses have the advantage of increased statistical power since they consider large numbers of workers;[73] however, the heterogeneity of the cohorts (in the quality and completeness of data, the nature of work done at different facilities, and the types of exposures received at the facilities) raises concern about pooling.[74] A report by Gilbert et al. on these pooled analyses noted a negative association between external radiation and leukemia, and no association between radiation and all cancer mortality.[71] Dose response associations were reported to increase for deaths occurring at older age among Hanford and ORNL workers, which the authors interpreted as evidence of "biases in the data that are not well understood." Gilbert et al. suggested that, "it is possible that smoking patterns could differ in early and later birth cohorts."[75] Since doses received at older ages can only be associated with cancer mortality at older ages however, changes in dose response associations with age at risk are difficult to distinguish from changes in these association with age at exposure.[67]

Kneale and Stewart also reported on analyses that included workers from ORNL and Hanford, as well as at three other DOE facilities.[17] They concluded that when time-related factors were considered, a positive association existed between radiation dose and cancer mortality among workers at each facility. However, significant differences existed in radiation-cancer associations between the cohorts, suggesting that pooled analyses may be inappropriate because of the heterogeneity between cohorts. For workers at ORNL the association between radiation and all cancer mortality was strongest when considering cumulative dose received after age 45 under a 21 year lag

assumption; for workers at Hanford this association was strongest when considering doses received after age 62 under a 17 year lag assumption.

Another pooled analysis considered cancer mortality among workers at nuclear facilities in the United States, United Kingdom, and Canada. United States workers were employed at ORNL, Hanford, and Rocky Flats. Cumulative radiation dose was negatively associated with all cancers except leukemia, and positively associated with leukemia excluding chronic lymphocytic leukemia (CLL) (2.18 % per Sv); in all cases associations were smaller than those derived from extrapolation from A-bomb survivors.[7]

Studies of the effects of cumulative external radiation dose and cumulative internal exposure to alpha-radiation among workers at uranium processing facilities have considered differences in dose response associations for workers hired at different ages. The relative risk of lung cancer among uranium processing facility workers has been observed to increase with increasing external radiation dose only among workers hired after age 45.[22, 76]

Studies of Radiation Health Effects Among Workers at ORNL

The association between radiation and cancer mortality among ORNL workers has been the subject of a number of analyses, in addition to the pooled analyses described above (Table 1.1). Abd-Elghany examined the relationship between total cancer mortality and low dose radiation in a nested case-control study of 423 ORNL workers who died of cancer, and 846 matched controls.[77] These analyses suggested that larger external radiation doses were accumulated among those who died of cancer than among those who did not; and, these differences were greater among workers hired at older ages than among workers hired at younger ages. In an analysis which compared workers who had any recorded external radiation dose to workers who had no recorded dose, odds ratios increased with age at hire from 0.64 for those hired

before age 25 years, to 1.15 for those hired ages 25-39, to 1.44 for those hired at ages >=39 years.

Checkoway et al. conducted SMR analyses among 8375 white male workers hired at ORNL between 1943 and 1972.[78] As in other DOE cohorts, all cause and all cancer mortality for these workers were lower than expected when compared to the general population;[12] however, elevated SMRs were observed for leukemia, cancer of the prostate, and Hodgkin's disease. Standardized rate ratios for leukemia increased with increasing external radiation dose and with longer latency assumptions, although no deaths were observed among those receiving the highest doses.

Table 1.1 Studies of Workers at ORNL

Author, Year	Study Population (number of workers)	Period of Follow-up	Analyses
Elghany, 1983	All Males Hired 1943-77 (1269)	1943-1977	Case-Control Study
Checkoway, 1985	White Males Hired 1943-72 (8375)	1943-1977	SMR analyses
Frome, 1990	White Males Hired 1943-47 at ORNL, Y12, K25 (28,008)	1943-1977	Poisson Regression
Wing, 1991	White Males Hired 1943-72 (8318)	1943-1984	Poisson Regression
Gilbert, 1992	White Males Hired 1943-72 (8307)	1943-1984	Mantel Haenszel
Wing, 1993	White Males Hired 1943-72 (8307)	1943-1984	Poisson Regression
Wing, 1995	White Males Hired 1943-72 (8307)	1943-1990	Poisson Regression

Frome, et al. examined the mortality experience of 28,008 white male Oak Ridge workers employed during World War II (1943-47).[79] The study included workers employed at ORNL as well as at uranium production facilities at Oak Ridge (Y-12 and K-25). A trend of increasing SMRs for all cause mortality with increasing years of follow-up was observed, primarily due to lung cancer and respiratory disease. Regression analyses examined associations between radiation exposure and mortality. Due to the poor monitoring of radiation exposure in the early years of operation, radiation exposure was considered as either exposed or unexposed. Relationships

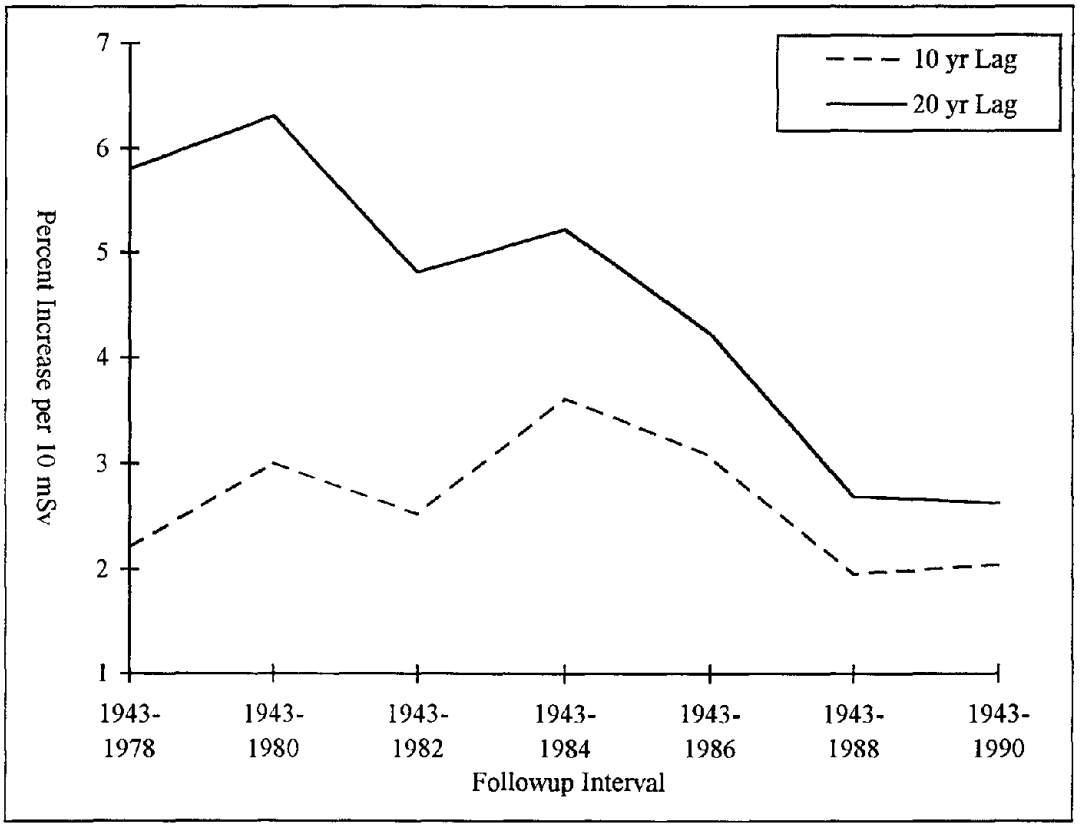
between radiation exposure and all cancer, lung cancer, and other cancer mortality were positive although the estimated associations had large standard errors.

Wing et al. examined the association between radiation and cancer mortality among ORNL workers hired between 1943 and 1972 with vital status follow-up through 1984.[19] Leukemia mortality was elevated in the cohort when compared to the general population. Examination of dose response associations between radiation and mortality among white male workers revealed that all cancer, lung cancer, and leukemia exhibited positive associations with external radiation dose. Associations were largest in magnitude for leukemia, intermediate for lung cancer, and smallest in magnitude for all cancer mortality. The magnitude of associations increased with longer lag assumptions. A 4.94% increase in all cancer mortality per 10 mSv dose was reported under a twenty year lag assumption.

Gilbert also examined associations between radiation and mortality among white males employed at ORNL. While reporting results similar to Wing et al., Gilbert noted that dose response associations were of larger magnitude for smoking-related cancers than for other cancers, and that dose response associations were positive for mortality due to circulatory disease and respiratory disease, suggesting confounding due to smoking.[80] Further analyses by Wing et al, addressed potential confounding due to cigarette smoking,[81] as well as confounding due to occupational exposures other than radiation.[82] Wing et al. noted that the association, reported by Gilbert, between radiation dose and mortality due to circulatory disease was due to a failure to control for socioeconomic differences in the cohort. Furthermore, contrary to expectations about confounding due to cigarette smoking, associations between radiation and cancer mortality were smaller in magnitude for lung cancer mortality than for smoking related cancer sites other than the lung; and, radiation-cancer associations exhibited a strong sensitivity to lag assumptions.

Preliminary analyses, reporting on vital status follow-up through 1990, noted that the magnitude of the radiation-cancer dose response relationship had diminished with additional follow up.[32] The SMR for leukemia was less elevated than in earlier reports, and when considering a 20-year lag assumption, the magnitude of the dose response association for the association between radiation and all cancer mortality was approximately half of the value reported for vital status follow-up through 1984. The association between radiation and cancer mortality was very small prior to 1977; rose from 1977 through 1984; and declined after 1984 (Fig. 1.1). Wing et al. suggested that further analyses should investigate whether these trends in dose response associations with follow-up could be explained as a consequence of differences in the effects of radiation received at different ages.

Figure 1.1. All Cancer Dose Response, Follow-up 1977 through 1990, 20 Year Lag



Conclusion

Recent national and international committees have reported that the effects of exposure to ionizing radiation are greatest when received by the very young and decrease when exposure is received at older ages.[3, 27] However, an alternative description suggests, to the contrary, that sensitivity to the effects of radiation may be greatest at very young and very old ages, with radiosensitivity at a low point for adults in their 20s and 30s.[16] This dissertation investigates associations between low level radiation and cancer mortality with attention to potential differences in the relative effect of radiation with older adult age. Understanding the effects of low level radiation exposure, and potential changes in these effects with age, is necessary for an evaluation of the consequences of environmental, occupational, and medical exposures to low levels of radiation.

Chapter Two - Materials and Study Variables

Overview

This chapter describes the study setting and the collection of data used for these analyses. The difference between the *Checkoway cohort* considered in our preliminary analyses, and the *expanded cohort* considered in subsequent analyses, is discussed. The methods used for ascertainment of vital status and collection of cause of death data are described, as are the methods used for collection of data on external radiation exposures received at ORNL. Our choice of demographic and employment variables is discussed with reference to previous research on this cohort and expectations from the literature about associations between sociodemographic variables and cancer mortality.

Study Setting

In December 1941, the United States government began to invest heavily in the creation of an atomic weapon. In the preceding year, U.S. and British scientists had convinced themselves that a rare isotope of uranium could be separated, gathered, and used in a chain reaction to release tremendous amounts of energy. The government authorized the rapid construction of full-scale, secret production facilities for this enriched uranium.[83, 84]

The U.S. Army was in charge of the construction project under the direction of Brigadier General Leslie R. Groves. In September, 1942, Groves approved the purchase of 59,000 acres in rural, East Tennessee in order to start construction of the massive compound originally named Clinton Laboratory (later renamed Oak Ridge National Laboratory). The site was to include facilities for production of enriched uranium, an experimental pile to produce plutonium, and research laboratories. Construction began in the winter of 1942, and by April of 1943 the facility was enclosed in its barb wire fence.[85]

The Du Pont Co. was contracted to build and operate an air-cooled experimental pile (at the X-10 facility), a chemical separations plant, and supporting laboratories at the Tennessee facility. Many of the workers coming to the facility were from out of town; most of the researchers came from the Metallurgical Laboratory at the University of Chicago, while the industrial and managerial workers came to Oak Ridge from other Du Pont facilities. ORNL was created as a facility for research and development of the atomic bomb, and the atomic pile there was used to create small amounts of plutonium. Since World War II, the ORNL facility has been used for research in the chemical, physical, and biological sciences.

Cohort Definition and Rationale

When reviewing these study results attention should be given to the difference between the two cohorts which were examined.

- The *Checkoway cohort* (n=8,307) included all white males, hired at ORNL between January, 1943 and the end of 1972, who had worked at least 30 days, had known dates of birth and hire, and for whom there was no record of employment at any other Department of Energy facility. This cohort was first defined by Checkoway et al., and has been examined by other researchers with small changes over time in cohort definitions.[17, 19, 71, 78] Detailed information on vital status follow-up, employment, demographic, and job characteristics has been reported previously.[78, 82, 86]

- The *expanded cohort* (n=14,095) included all employees hired at ORNL between January, 1943 and the end of 1972 who had worked at least 30 days, had known gender, race, and dates of birth and hire, and had two years or less of missing external radiation dose data from employment at other DOE facilities.

Preliminary analyses, in which we developed our analytical methods, were conducted using the Checkoway cohort. These preliminary analyses allowed us to: verify that our methods for generating person-time data produced regression estimates comparable to those previously reported; compare the results of regression analyses which considered latency and age at exposure to estimates previously reported; and then, to assess the effects on these dose response associations of using an expanded cohort definition.

The expanded cohort includes women, non-whites, and workers with employment at other DOE facilities. Women and non-white workers were included in order to

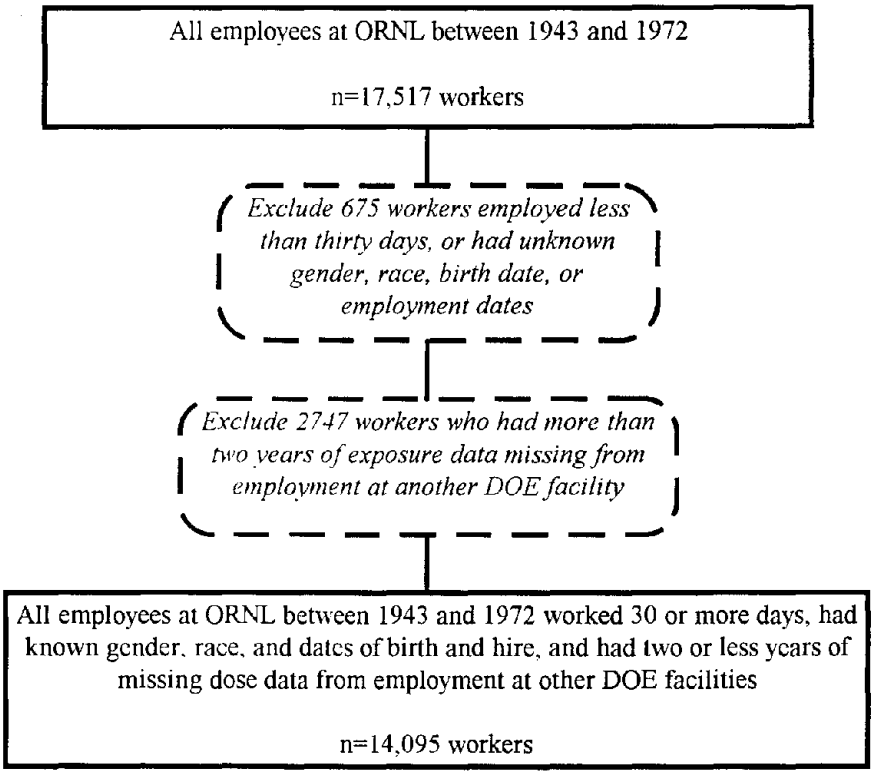
examine the effects of low level radiation among a cohort which was representative of the complete workforce. Workers had been excluded from past studies because they were known to have been employed at other DOE facilities. Employment at other DOE facilities was a common occurrence among workers at ORNL because of the location of two other major DOE facilities at Oak Ridge (K-25 and Y-12). The three Oak Ridge facilities were operated by the same contractors after 1947, so movement of personnel across facilities occurred. ORNL workers were also employed at the Savannah River Plant, Hanford and other DOE facilities.

By expanding the cohort definition, however, concerns were raised about potential differences in data which could lead to biases or confounding. Occupational exposures and radiation monitoring programs differed significantly between facilities; and, with inclusion of nonwhite and female workers, the completeness of vital status ascertainment decreased. Consequently, we conducted preliminary analyses among the Checkoway cohort, which has the most complete data. We then assessed whether associations between low dose radiation and cancer mortality differed when we used our expanded cohort definition.

Enumeration of the Expanded Cohort

Between 1943 and 1972, 17,517 workers were employed at ORNL. From these workers, 675 were excluded because they were employed less than thirty days, or had unknown gender, race, birth date, or employment dates. An additional 2,747 workers, who also had been employed at another DOE facility and had more than two years of exposure data missing from that employment, were excluded. These exclusions left 14,095 workers (80.5% of all workers employed between 1943 and 1972) eligible for inclusion in the study cohort (Figure 2.1).

Figure 2.1 Enumeration of the Expanded Cohort



Vital Status Ascertainment and Loss to Follow-up

Vital status follow-up of the ORNL cohort has been conducted by the Oak Ridge Associated Universities, Center for Epidemiologic Research. Vital status was determined from a variety of sources, including three searches of Social Security Administration (SSA) records during the 1970s and 1980s, records of the Health Care Financing Agency, Tennessee Department of Motor Vehicles, a credit and pension benefits research group, the benefits department of the contractor currently operating the facility, personnel records, obituaries, and the National Death Index (NDI), which includes all deaths in the United States beginning in 1979.[86]

Initially, SSA records were the primary resource for ascertaining vital status. Social Security Administration records allowed identification not only of deaths, but also identification of workers who were still alive. With access to SSA records discontinued in 1987, searching the NDI became the preferred method for updating vital status. A search of the NDI for the years 1979-1990 was conducted in 1992 for all workers not already known to be deceased or currently employed. The NDI has been shown to identify essentially all deaths in the United States.[87-90] When a subject's social security number is available, the NDI has been reported to accurately identify 97% of known deaths; overall the Index is reported to identify 93% of deaths, with sensitivity varying by race and gender.[89, 90] In a comparison of the NDI to the SSA system for ascertainment of vital status, conducted among the white male workers at Los Alamos National Laboratory, the NDI correctly identified 99.5% of the deaths identified by SSA for the period 1979-1983.[91]

Individuals known to be alive as of 1 January 1979 or later were assumed to be alive at the end of the study if the NDI gave no indication that they had died. Workers whose vital status was unknown in 1979, and did not have a death indication from NDI, were counted as unknown vital status. For workers with unknown vital status, person-time was counted only until the date of last contact (typically, the date of termination of

employment at ORNL), thereby including all available person-time of observation without making assumptions about the mortality of workers after loss to follow-up.[92]

Certification of Cause of Death

Information on cause of death was collected through retrieval of death certificates from the vital registration offices of all 50 states, New York City and the District of Columbia. Coding of cause of death information was done by a qualified nosologist according to the eighth revision of the International Classification of Diseases adapted for use in the United States (ICDA). The underlying cause of death was coded as well as any cancer that appeared on the death certificate that was not the underlying cause of death; recording information other than the underlying cause of death was done to increase the sensitivity of detection of cancer causes of death.[82]

Annual External Radiation Dose Data

External radiation monitoring data for the period 1943-1985 were available for this study from records at ORNL. External radiation doses were estimated for years of employment at ORNL with missing dose data using a hierarchical decision algorithm that first relied on the worker's dose estimates in adjacent time periods within one or two years of the missing year, and, if those were not available, relied on average values for similar workers or, in cases where department information was not available, all workers. At ORNL the vast majority of missing doses were estimated from worker's own data in adjacent years. This "nearby" procedure avoids making a most extreme assumption about the missing dose (that no exposure occurred in the year with missing dose data) and provides a complete set of annual dose estimates with a minimum of assumptions.[93]

Dosimetry data from other facilities, including Y-12, K-25, Hanford, and the Savannah River Plant were merged with the ORNL records. Workers with more than two years of missing external dosimetry data during employment at other DOE facilities were excluded from the expanded cohort.

Changes over time in External Radiation Dosimetry at ORNL

Health physicists at ORNL developed much of the technology for radiation dosimetry; consequently ORNL is one of the occupational cohorts with the longest and most complete histories of radiation dosimetry. Monitoring began at ORNL in February, 1943 and continues through to today.

Occupational exposure to radiation at Oak Ridge is described as beginning when the X-10 graphite reactor went critical on November 3, 1943. In December of that year, irradiated fuel was removed from the reactor for processing. About fifty percent of the workers in the Checkoway cohort were monitored for external exposure in 1943; by 1944 eighty-six percent of the cohort was monitored, and over ninety-eight percent

of the cohort was monitored by 1948.[94] By November, 1951 all ORNL workers were required to have a film badge, and in September, 1953 this film badge was incorporated into a security badge that was required to be worn at all times.[86] A computerized file contains a record of the measurements for each worker from February, 1943 through December, 1985; this file contains nearly 700,000 entries for over 28,000 monitored workers.[86]

Measured external ionizing radiation exposures at ORNL are characterized by a spike of high annual exposure in 1944, followed by a rise from the late 1940s to the late 1950s, and then a gradual decline in measured exposures to the end of the study period.[19] Changes in recorded dose over time may, in part, reflect changes in production processes at ORNL. Changes in recorded dose over time may also be related to changes in the techniques used for measuring external radiation exposure,[95] and in the frequency of reading dosimeters. The different techniques can be summarized as follows. Pocket ionization chambers were used from February, 1943 through May, 1944, film badge dosimeters were used from June, 1944 through December, 1975, and thermoluminescent dosimeters (TLDs) have been used since January, 1976.[96]

In the early years of the radiation monitoring program, dosimeters were read frequently. Pocket ionization chambers were read daily, and film badges were read weekly until 1956. The frequent reading of dosimeters was not well-suited to detecting low doses of occupational radiation exposure, since when monitoring devices were read frequently a worker could have been exposed to radiation yet not received a sufficient amount to be detectable.[97] After 1956 film badges were read quarterly or annually. For doses received below the minimum detectable dose (MDD) the practice for recording MDDs appears to have changed over time; in some periods a zero dose appears to have been recorded while in other periods doses between zero and the detection limit may have been recorded.[94, 98]

There are further reasons to that recorded doses could underestimate the actual whole body dose received. When interpreting the dose recorded on the badge, it is assumed that the radiation exposure occurred at a horizontal angle (the angle of exposure can affect the dose recorded by the badge) to the front of the worker.[99] However, in actuality it is rare that a worker is exposed to a uniform radiation field.[100] Some individual behaviors, which might follow from incentives to avoid documentation of higher doses, could also lead to underestimation of radiation exposures. It has been suggested that some workers might have removed their badges before performing tasks which entailed high exposures; this action would have been taken in order to ensure that their recorded exposures were below standards which would otherwise require them to stop work.

These problems could lead to underestimation of doses received by workers in all dose groups, or to differential underestimation with respect to exposure;[94] consequently, underestimation of dose could lead to under- or over-estimation of the effects of low level radiation. As well as underestimation of doses, some factors may have led to non-differential misclassification of exposures; these include laboratory errors in readings dosimeters, and errors in correctly matching the large number of dosimetry records to the correct workers.[101]

Changes in dosimetry techniques are not just relevant to considerations of the magnitude of radiation-cancer dose response estimates. These changes are also relevant to considerations of trends in dose response estimates over calendar time. Changes over time in the (under)estimation of doses, for example, could lead to changes in estimates of dose response associations. Also, temporal trends in the minimum detectable dose could affect the comparative magnitude of dose-response estimates under differing lag assumptions. Since longer lag analyses are more heavily dependent on dose measurements in earlier calendar years, if problems of dose

underestimation were larger in the early years of operation, smaller doses could be associated with larger observed effects. To investigate concerns about potential underascertainment of exposure in the early years of ORNL's operation, we conducted a series of analyses considering workers hired in earlier and later historical periods.

Internal Radionuclide Exposure

We considered internal exposure to radionuclides as a potential confounder of the association between external radiation and cancer mortality. Internal deposition of radionucides was believed to be uncommon and the levels of exposure were believed to be much less substantial than exposures to external radiation.[86] However, understanding of the health effects of internal deposition of radionuclides is limited.[74, 102] Previous studies have suggested that occupational exposure to plutonium may lead to excess cancers, as well as measurable increases in chromosomal aberrations;[49, 50, 74, 103, 104] and, previous analyses of workers at ORNL suggest differences in the mortality experience of workers who were monitored for internal radionuclide deposition.[19] At ORNL, workers who were monitored for internal exposure had lower SMRs than the entire study cohort for all cause mortality, all circulatory disease, and external causes; however, workers who were monitored for internal exposure had larger SMRs than the entire cohort for lung cancer, lymphosarcoma, and leukemia.[19] Consequently, although the level of exposure from internal deposition of radionuclide is expected to be small, attention was given in our analyses to the available data on internal radionuclide monitoring.

The decision to monitor a worker for internal deposition of radionuclides was determined by health physicists at ORNL, and indicated that the worker was at risk of contamination.[86] Monitoring consisted of regular urinalysis, and potentially fecal monitoring as well. Since the methods for detecting radionuclides by internal monitoring are poor, we considered evidence that the worker was monitored as an indication of a job at higher risk of internal contamination. An important limitation of these data is that internal exposure monitoring was not conducted prior to 1951.[86] Consequently, in the early years of operation there is no way to assess confounding effects of internal exposure.

Employment Status

A common observation in studies of workers in the nuclear industry is that nuclear workers tend to be a group of people with good health and low mortality rates compared to the general population.[12] This has been described as evidence of a 'healthy worker effect', in which people with good health are selected for employment in a particular industry.[92]

In analyses which compare the mortality rates of workers within an industry by level of exposure, selection factors related to a worker's health may be associated with their level of cumulative exposure.[105] For example, physical examinations might be required for workers to perform jobs in radiation exposed areas, and jobs involving radiation exposure might also require special education which could lead to socioeconomic (and related mortality) differences between exposed and unexposed workers.[106] Such selection processes suggest that workers receiving radiation exposure might have lower baseline mortality rates than other workers within the same industry, biasing dose response associations downward.[107]

Short term employment in an industry may be associated with higher mortality rates than long term employment, especially in blue collar jobs in which short term employment may be associated with lower socioeconomic status. Short term employment is also associated with low cumulative exposure; hence, if workers with short term employment have poorer health this could lead to a downward bias in estimates of dose response relationships.[92] Workers employed less than 30 days have been excluded from our analyses.

Similarly, when workers develop poor health they tend to leave, or be selected out of, the workforce, while those with good health remain employed and may accumulate exposure. Such patterns of employment selection might also be expected to lead to a downward bias in dose response associations. However, in analyses which investigate

a lag assumption, only those exposures received several years before the onset of the disease are considered. In a lagged analysis, it is less likely that differences in cumulative dose between workers would be due to health-related selection out of the workforce.[108] We considered analyses with five, ten, and twenty years lag assumptions.

The converse was also considered: healthier workers may tend to be selected into the workforce.[109] Workers who were recently hired may be expected to have very good health, and are necessarily assigned to the lowest dose group in a lagged analysis.[82] However, the relatively better mortality experience of a recent hire cohort compared to others in the industry tends to decline with longer follow-up. In our analyses, all workers had at least eighteen years of follow-up; consequently these differentials would be expected to be minimized.

An exception to the observation that mortality differentials between hire cohorts tends to decline with increasing follow-up, however, is that this differential tends to decline only after workers exit the workforce.[108] Actively employed workers, with longer time since hire, tend to be healthier than workers who terminated employment (and these workers tend to have higher cumulative exposures). This has been referred to as a 'healthy worker survivor effect' which may lead to an underestimation of dose response relationships in an occupational cohort.[110] One method for limiting the effect of these selection processes is to consider active employment status as a time dependent variable; and consider an interaction so that with increasing age, the mortality differential between actively employed workers and terminated workers may differ.[111, 112] Arrighi evaluated methods for controlling employment selection factors among ORNL workers, examining associations between external radiation and mortality due to lung cancer, circulatory disease, and accidents. Arrighi concluded that the use of an age-specific indicator of active employment status was useful,

although perhaps not entirely sufficient, to adjust for this "health worker survivor effect."[110]

Paycode

When examining exposure-disease associations in a working population it is important to recognize the role of socioeconomic status as a determinant of mortality.[113] Overall, the mortality experience of workers at ORNL was better than the mortality experience of persons in the general population.[19] In internal comparisons of mortality among workers at ORNL, it must be further considered whether differences in cancer mortality rates by exposure level are confounded by socioeconomic differences between employees.

Our analyses examined paycode as an indication of socioeconomic differences in the workforce.[82] Paycode was based on the worker's pay schedule when hired. Among male workers, monthly-paid workers were mostly in professional positions which require a high level of education; non-union supervisors were paid weekly; and, unionized blue-collar workers were paid hourly. Female workers were most often paid weekly; weekly-paid women were often employed in different jobs than weekly paid men, and typically were assigned job titles such as clerical worker. Hoffmann examined the association between mortality and paycodes among Oak Ridge facility workers and reported that important differences existed between paycodes in the mortality experience of ORNL workers.[114]

Age, Birth Cohort, Gender, Race, and Facility

Previous analyses of workers at ORNL, similar to analyses of people in other study populations, have established age and birth cohort as two factors that are important determinants of cancer mortality, [51, 57, 115] that may also be associated with levels of cumulative dose. Consequently, similar to previous analyses of this cohort, we have attempted to control for these potential confounding factors in our analyses.

Following previous analyses,[19, 32, 82] we examined the use of a continuous term in our regression models to describe changes in cancer mortality rates with age. In previous analyses the association between age and cancer mortality was found to be described adequately using a continuous term for age; this simplified analyses, since it was not necessary to include a large number of indicator terms for age categories. In order to control for age using a continuous term, it was necessary to specify the shape of this association. As in previous analyses, cancer mortality has been described using a Weibull function (log-log association between age and cancer mortality).[19, 71, 80]

Age-specific mortality rates are not simply fixed consequences of aging, but rather exhibit significant historical trends (as do patterns of annual external radiation exposure at ORNL). We considered birth cohort in our analyses by including categorical terms for year of birth.

The inclusion of women, non-white workers, and workers with employment at other facilities led to our examination of these factors as potential confounders in our analyses. Women and non-white workers may have different age-specific mortality rates than white males for numerous sociobiological reasons; furthermore, at ORNL, cumulative external radiation dose (under almost any hypothesized lag or age at exposure weighting scenario) is also related to race and gender. We also examined an indicator of whether a worker was employed at ORNL only, or was employed at other DOE facilities. Changing jobs may be associated with differences in health status,

while employment at other DOE facilities may be associated with differences in exposures as well as differences in the quality of radiation dosimetry data.

Unmeasured Potential Confounders

Workers at ORNL were potentially exposed to many agents other than external ionizing radiation. Other potentially carcinogenic occupational exposures at ORNL include benzene, organic solvents, and powerful electromagnetic fields.[86] However, little quantitative data are available on these exposures, and an evaluation of indicators of potential exposures, such as job titles,[82] was beyond the scope of this dissertation.

Cigarette smoking has been suggested as another potential confounder of concern,[80, 116] although previous analyses have not supported this contention.[81] It has been argued from epidemiologic principles that smoking is unlikely to be an important confounder of dose-response relationships in occupational studies;[117-119] and, previous analyses of workers at the Hanford nuclear facility have found no evidence of an association between tobacco use and external radiation dose.[120] Several analyses in this dissertation assess confounding due to cigarette smoking indirectly by examining the association between radiation and lung cancer, cardiovascular disease, and non-malignant respiratory disease.[121]

Outcomes of Interest

The outcome of primary interest in these analyses was all cancer mortality. In contrast to studies of people exposed to medical irradiation of a specific organ, this study examines a cohort of workers with whole body exposure to radiation. Since radiation is thought to be a general mutagen to chromosomes across cell types,[4] whole body exposure to radiation may affect the risk of mortality from most types of cancer.[33]

Furthermore, since the etiology of radiation-induced cancer is poorly understood, the biological rationale for studying all cancers may be as strong as the rationale for studying an a priori defined group of radiosensitive cancers. Previous attempts to define a group of radiosensitive cancers have been found to be inconsistent between study populations.[63, 122] For example, Stewart and Kneale derived a list of radiosensitive cancers from an ICRP publication which included cancers of the pharynx, digestive system, breast, lung, thyroid, and lymphatic and hematopoietic cancers. Subsequent critics, however, noted that in other populations, including the LSS of A-bomb survivors, the relative risk estimate for this group of radiosensitive cancers was slightly lower that the estimate for cancers excluded from this group.[122]

Previous studies of radiation-cancer associations among workers at ORNL have examined all cancer mortality and provide evidence of an association in this population. Since the research questions being investigated in this study were partly motivated by these previous analyses, this provides further rationale for examining of all cancer mortality. Finally, while death certificate data are reasonably accurate for identifying all cancers as a group, they are a less sensitive tool for making distinctions between specific types of cancer; consequently, consideration of deaths due to particular cancers may not strengthen this study.[3, 123] To the extent that radiosensitivity differs by cancer type, our results reflect an average of effects between more and less radiosensitive cancers.

In order to evaluate questions about potential confounding (in particular, due to cigarette smoking), however, dose response analyses were conducted for a limited number of cancer and non-cancer causes of death (Table 2.1). Specific cancers, such as female breast cancer and leukemia, which were of interest because of previous reports of radiosensitivity, occurred too rarely to allow analyses of dose response associations.

Table 2.1 Causes of Death Examined and Associated ICD Codes, Eighth Revision

Cause Of Death	ICD Codes	Number of cases
All Cause	vital status='D'	3269
All Cancers	140-209	879
Lung Cancer	162	245
Ischemic Heart Disease	410-414	976
Nonmalignant Diseases Of The Respiratory System	460-519	167

Categories based on combinations of these groups were also considered; these included all causes except cancer, and all cancers except lung.

Chapter Three - Analytical and Statistical Methods

Overview

This chapter discusses the analytical and statistical methods used in these analyses. We begin with a discussion of time-related variables, and then describe our methods for examining cumulative external radiation dose, latency, time-since-exposure, and age at exposure. We next discuss our methods for creating tables of person-time and events, and the assignment of specific values to categories of dose and age for use in our regression analyses. Finally, we discuss the regression models used in these analyses and the influence of modeling assumptions on our estimation of radiation-cancer associations.

Time-related Factors

In these analyses we examine cancer mortality rates in a population of workers, some of whom received radiation exposure, and some of whom have been followed to the end of their life. To estimate the effects of radiation on cancer mortality, we first describe cancer mortality rates in terms of demographic and employment characteristics of the workforce. The effect of radiation, then, can be expressed as the absolute, or the proportional, difference in cancer mortality rates among the exposed when compared to the unexposed.[124]

Since the level of radiation dose differed between workers, we evaluated dose response associations, estimating the percent change in cancer mortality per unit dose.[2] Dose was examined in a time-dependent fashion by calculating cumulative dose; since using a cumulative measure of exposure raises the possibility of time-related confounders, our analyses examined factors which might relate employment or demographic factors to a worker's cumulative dose.[125, 126] Furthermore, we were interested in examining time-related factors which might modify the effects of exposures.[92] We examined lag assumptions, time since exposure, and age at exposure.

In the previous chapter we discussed our handling of time-related study covariates. In this chapter, we address our use of cumulative dose, our analytical methods for examining differences in the effects of doses received at different periods of exposure (defined by age at exposure and lag assumptions), our use of relative risk models, and our evaluation of multiplicative and additive relative risk functions to describe dose response associations.

Cumulative External Radiation Dose

Use of cumulative dose as a measure of exposure carries with it a number of assumptions, including that: separate doses of radiation act independently; the effect of separate doses is cumulative, even for the lowest dose rates of exposure; similar exposure intensities at different ages have similar consequences; and, prolonged exposure is not required for disease induction.[16, 92] Alternatives to examining cumulative dose include examining the effects only of peak doses or periods of high dose rate exposure (for example positing that very low doses have no effect).[127] However, at ORNL, exposure patterns were complex; and, in general, the effects of exposure intensity and duration are difficult to distinguish from the effects of cumulative exposure. Consequently, in these analyses we relied on cumulative radiation dose as a simple method for summarizing workers' exposure histories.

In these analyses, cumulative dose was categorized in order to allocate person-time and events within tables. We calculated cumulative dose as the time-dependent summation of annual recorded doses; person-time and events were categorized by seven levels of exposure, as follows: 0, >0-20, 20-40, 40-60, 60-80, 80-100, 100+ mSv. Although the first categories may be too narrow to be useful for identifying differences in radiation risk, comparisons of risk between the 0 group and the "almost 0" groups are of interest in relation to questions about selective differences between workers who are never exposed, many of whom have shorter durations of employment or did not enter potentially exposed jobs, and those who were employed in jobs with potential for radiation exposure but who did not have recorded exposures above very low levels.

The appropriateness of this categorization was assessed by examining the distribution of person-years and events within each of the dose groups, with attention given to differences in these distributions under different assumptions about latency and age at exposure. Since records of external doses were reported as annual doses, in order to

calculate cumulative dose in a time-dependent fashion we assumed that the entire annual dose was received at the midpoint of each calendar years (July 1st).

Latency and Time windows

Under the premise that there is typically a latency period of several years between a relevant exposure and the clinical detection of a cancer (or death due to cancer), exposures are often 'lagged.' In our analyses, to consider a lag assumption of 'y' years, we assigned person-time and events according to the level of cumulative exposure achieved 'y' years earlier. It is assumed that ignoring those exposures immediately before the diagnosis of disease (or death) removes irrelevant exposure information which might lead to a biased estimate of the exposure disease relationship.[128]

Since latency periods are likely to differ between people, the best fitting lag assumption may be considered to represent an average latency. Latency periods may differ for different types of cancer, and be modified by exposure rates;[129] when considering time trends in dose response associations, the best fitting lag assumption may be dependent on historical changes in the distribution of cancers by type, and may differ between historical periods in which there are differences in exposure rates.[130]

The effect of misspecifying lag assumptions may differ for different groups of workers within a cohort. To the extent that one misspecifies a lag assumption, suggesting a lag which is shorter than it should be, one includes doses that are not relevant. For workers with the shortest period of follow-up, and for those workers most recently hired, such misspecification will lead to greater bias in estimates of dose response associations (since the majority of their follow-up time occurs during the actual latency period).

Analyses of time related factors can be further complicated by assessing time since exposure as well as lag assumptions.[51] For a given age at risk, not only might recent exposures be irrelevant (due to latency considerations), but very distant exposures may also be irrelevant (for example, due to death of all initiated cells and their progeny). It has been proposed that an empirical induction time can be examined

by the use of time windows.[92] Thus, time windows that take into account both lag and time-since-exposure allow investigation of potentially critical time periods of exposure. In our time window analyses, exposures within the time window are weighted as 1, and outside exposures are disregarded--assigned a weight of zero.[57] Only simple step functions were considered in these analyses of lag and time since exposure.

It is not clear, however, that doses received in the distant past are etiologically irrelevant to the onset of disease.[4] While some studies suggest that the excess relative risk of leukemia declines several decades after radiation exposure, the effects of radiation on the relative risk of all cancer mortality continues in most studies after very long latencies, with effects persisting for up to forty years after exposure.[4] Some evidence suggests that the excess risk of all cancer mortality following radiation exposure may increase faster over time than the increase in cancer rates with age among the unexposed,[4] which would suggest that with longer lag assumptions, the excess relative risk associated with radiation exposure may increase.

Age at Exposure

In an occupational setting, such as that at ORNL, radiation exposure generally occurs over many years and workers may be exposed over a range of ages. Consequently, examination of a fixed age, such as the age at hire or age at first exposure, is not sufficient for assessing differences in the effects of workers' exposures received at different ages.

We were particularly interested in the hypothesis that effects of exposure increase with older age. Our ability to examine the effects of exposures at very old ages was limited, however, since if exposure occurs at an older age, when the years of remaining life expectancy may be less than the minimum latency period, the excess risk associated with that exposure will approach zero. Within an occupational cohort, a further limitation of examining exposures received at older age is that employment generally ends around age 65; consequently, examination of the effects of cumulative exposure after age 60, or even age 55, is limited by the short period over which occupational exposures might be accumulated.

We investigated hypotheses about the effects of age at exposure by using methods which took account of the age at which exposures were received when allocating person-time and events by level of exposure.

Weighting Annual Doses by Age

One method we used for investigating age at exposure was to assign different weights to exposures received at different ages. The level of cumulative dose associated with a unit of person-time at any specific age, was the sum of the weighted annual doses received up to that age.

The approach of weighting exposures is common in studies of cancer mortality in relation to radiation or chemical exposures. For example, in order to take into account

a lag assumption, researchers often discount doses which were received during a period immediately preceding detection of a cancer. Discounting exposures may improve the fit of a dose response model by excluding etiologically irrelevant exposures. Analogously, we investigated the effects of assigning less weight to annual doses received at younger ages.

Among the workers at ORNL, we assigned an age to each calendar year of exposure. We determined a worker's age at July 1st of each calendar year of exposure and associated that age with exposures recorded for that calendar year. Each worker in the cohort has a recorded annual dose each year from 1943-1985. If the worker was not employed the recorded annual dose was zero.

Our first analyses investigating age at exposure used a step weighting function. Annual doses received before a critical age were weighted zero and annual doses received after that critical age were weighted one (weighting function 1, figure 3.1). We examined a range of critical ages using this model. Entirely discounting doses received at younger ages, however, seemed conceptually less plausible than gradually discounting doses which occurred at younger ages. So, we considered the following functions (figures 3.1, 3.2) for weighting dose received in a calendar year 'y' by the age at which the exposure occurred:

(1). Lifetime cumulative dose:

Weighted annual dose(y) = Annual dose (y) * w, where w=1.

(2). Step weighting function:

Weighted annual dose(y) = Annual dose (y) *w, where w=0 if age<critical age;
and, w=1 if age>=critical age.

(3). Linear weighting function:

Weighted annual dose(y) = Annual dose (y) * Age(y) / 45; bounded by 0,1.

(4). Quadratic weighting function:

Weighted annual dose(y) = Annual dose (y) * $(Age(y))^2 / (45)^2$; bounded by 0,1.

(5). Sigmoid weighting function:

Weighted annual dose(y) = Annual dose (y) * $(Age(y)/45)^k$ / $[(Age(y)/45)^k + (Age(y)/45)]$

The sigmoid weighting function (weighting function 5) is a ratio, which, for large values of k, approximates a step function similar to weighting function 1, however, there is a smooth gradation of weights across age.

Figure 3.1 Functions to weight annual radiation dose by age at exposure

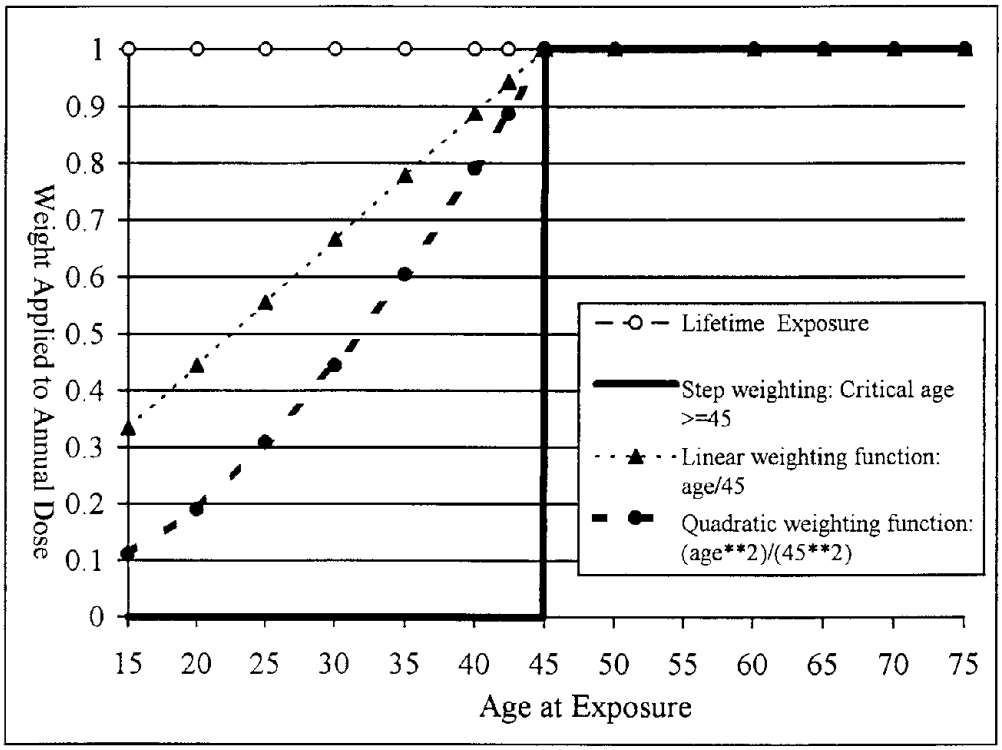
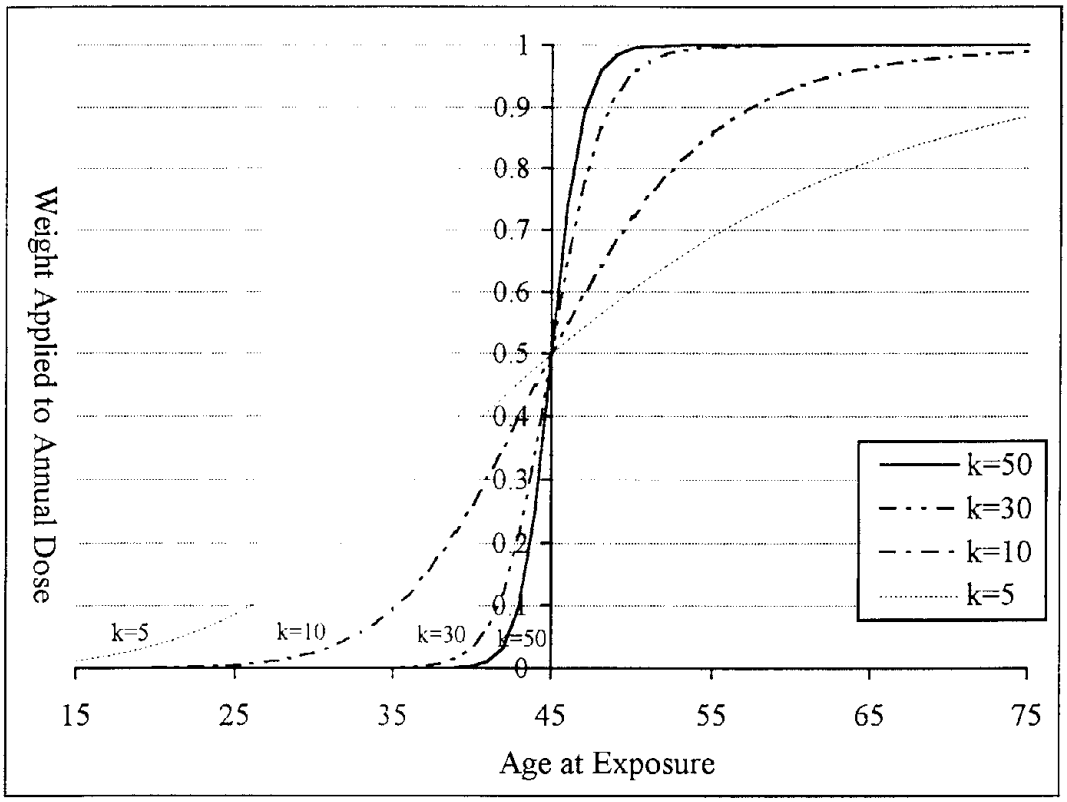


Figure 3.2 Sigmoid function to weight annual radiation dose by age at exposure.



Partitioning Cumulative Doses by Age

In order to conduct analyses in which we controlled for the effects of radiation doses received at earlier ages, we partitioned a worker's cumulative dose by the age at which exposures were received. Under this method, person-time and events are classified into two dose categories, indicating the level of dose accrued before, and after some critical age.

For example, consider partitioning cumulative dose at age 45. A table in which person-time and events were cross-classified by the levels of exposure received before and after age 45 would be examined. Person-time and events would be allocated according to the level of dose received after age 45 while also classifying the person-time and events according to the level of dose received before age 45. In such a table,

columns may represent the dose categories for exposures received before 45, and rows the categories for exposures received after age 45.

The pattern of radiation risk moving down a column would be the dose response pattern for exposures received after age 45 for workers, all of whom were in the same category of exposure received before age 45. Hypotheses can then be tested in order to assess whether row effects are homogenous across columns. This would assess whether the effect of exposure received after age 45 was modified by the level of exposure received before age 45; if it was not, then a single summary measure could be reported for the dose-response pattern for exposures received after age 45, controlling for exposures received before age 45. Finally, in a lagged analysis, person-time is associated with an exposure only a number of years after the dose was received. For example, under a ten year lag assumption, in the table described above, until age 55, all person-time would be attributed to the lowest level of dose received after age 45.

Creation of Tables of Person-Time and Events

Tables of person-years of follow-up and cancer deaths were created using a modified version of Pearce's person-time program, which tabulates each day from the date of first observation to the date of last observation for each person in the cohort within a multi-dimensional array.[131, 132] After the last day of observation, a person's vital status was assessed; if the person has died, a death was counted, classified by the same levels of the variables observed at the last day of observation. This method for making stratified person-time tables doesn't require rounding of person-years. A large number of stratifying variables were considered, many of which were time-related variables. Since this program does not round follow-up time, the level of each time-dependent variable (which in our analyses included age at risk, employment status, internal monitoring status, and cumulative dose) was calculated for each person-day of observation. A detailed description of this program is presented in the paper "A simple program to create exact person-time data in cohort analyses."[132]

Assignment of dose values to dose categories

In these analyses, study variables were categorized in order to tabulate follow-up and events within person-time tables.[133, 134] However, when conducting regression analyses of data in these tables of person-time and events, we examined continuous, rather than categorical, terms for age at risk and cumulative dose. To examine these factors using continuous terms, we had to associate specific values with age at risk and cumulative dose categories.

A simple method to associate specific values with dose categories would be to calculate the mean or median cumulative dose for each dose category, and use these values to fit a continuous term across dose categories. However, an overall mean is often not representative of the range of values within a group, particularly when a category is open-ended.

In our analyses, rather than assigning a single value to each dose category, we calculated the person-time weighted mean value for each dose group cross-classified by age, birth cohort, paycode, employment status, and internal exposure. This allowed us to assign each dose group a different value when cross-classified with each of the other variables--using what is referred to as the "cell-specific mean value."[135, 136] Cell-specific mean doses were calculated by summing the cumulative dose counted within each cell each day of follow-up; the mean dose for a cell, then, is the sum of the doses divided by the number of person-days of observation.

Compared to the overall mean for a category, values assigned to dose groups under this method better reflect the range of observed levels of cumulative dose. Furthermore, this method more closely approximates an analysis of ungrouped data, permits a wider range of dose values to which to fit a continuous term, and leads to analyses which are less sensitive to decisions about dose category boundaries.[135]

We calculated the cell-specific mean age in the same fashion in order to associate specific values with age at risk categories.

Absolute Risk and Relative Risk Models

Dose-response relationships may be evaluated using absolute risk or relative risk models.[137, 138] Our analyses used relative risk models, under which the excess risk of cancer persists on a proportional scale as cancer rates increase with age.[139] Relative risk models have been used in many analyses of cancer because of the epidemiological observation that cancer rates appear to be well described by such a model.[3]

Under a relative risk model, the increase in risk of cancer per unit of exposure is dependent on the spontaneous risk of cancer among those not exposed, and proportional to baseline cancer risks. In interpreting our dose response coefficients, a unit of radiation exposure is not simply associated with a fixed change in the absolute risk of cancer; rather it is associated with an increased relative risk of cancer that persists as the population ages and baseline cancer rates increase.

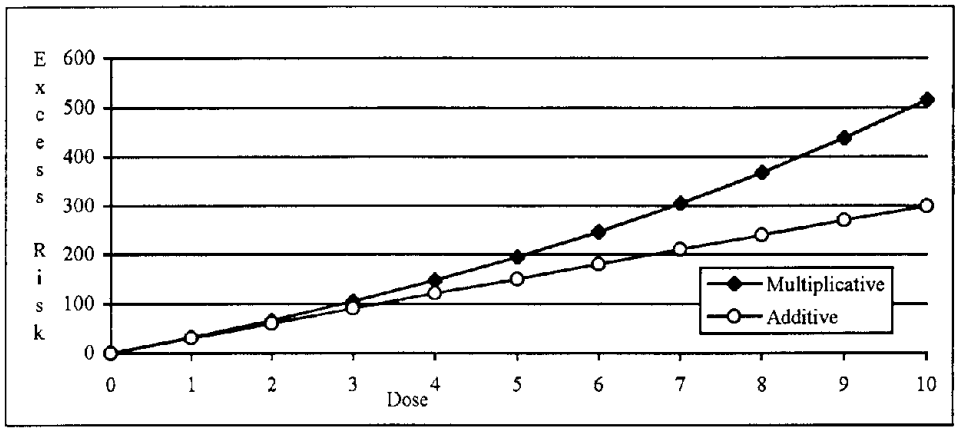
We were interested in evaluating modification of the radiation-cancer relationship by age at exposure; consequently, the distinction between absolute risk and relative risk models was important. Modification by age at exposure under a relative risk model, for example, might mean that an exposure received after age 45 under a ten year lag would lead to a larger relative increase in cancer mortality rates per rem per year after age 55 than an exposure received before age 45; and, under a relative risk model, this excess persists, on a proportional scale, even as baseline (or spontaneous) cancer mortality rates increase with age.

Forms of Dose Response Functions

Our analyses of radiation cancer associations evaluated two forms of the relative risk model: the additive relative risk model; and, the multiplicative relative risk model. When estimating the change in cancer mortality rate per unit cumulative dose, a mulitiplicative relative risk model assumes that exposure is exponentially related to the risk of cancer. The multiplicative relative risk model is of the form, $\lambda(Z,x) = e^{Z\alpha + \beta x}$, where the cancer mortality rate λ is considered in terms of a vector of covariates (Z) and radiation dose (x).[136, 138] A vector of parameter estimates, α, is associated with the covariates, and the parameter estimates β represent the association between cumulative radiation dose and cancer mortality. As cumulative dose increases, the risk of cancer mortality increases logarithmically, so that there is a linear relationship between dose and the log of risk.[138]

Alternately, under an additive relative risk model, as radiation dose increases the relative risk of cancer mortality increases linearly (Figure 3.4).[138] Using the same notation as above, an additive relative risk model is of the form $\lambda(Z,x) = e^{Z\alpha}(1 + \beta x)$. It should be noted that in terms of the previous discussion, these are both relative risk models; whether evaluating multiplicative relative risk or additive relative risk models, the excess cancer rate associated with exposure is proportional to baseline cancer rates.

Figure 3.3 Excess Risk per Unit Dose for Multiplicative and Additive Relative Risk Models



Estimates of the radiation-cancer dose response association in the LSS of A-bomb survivors evaluated both multiplicative relative risk and additive relative risk models. Additive relative risk models, which tend to yield higher risk estimates and wider confidence intervals, are more commonly used than multiplicative risk model; however, when evaluating the effects of low cumulative doses, the estimates of effect using either of these relative risk functions will be similar.

A range of functions can be considered which further change the form of the dose response pattern. One might investigate functions of the dose response pattern based on ideas about the underlying biological processes involved in the association between radiation and cancer mortality. For example, in the BEIR III report the dose response relationship was modeled as $F(D) = (\alpha_0+\alpha_1 D+\alpha_2 D^2)\exp(-\beta_1 D-\beta_2 D^2)$, where D is dose.[2] This model, which includes a negative exponential relationship with dose, allows for cell sterilization as a competing process with cell initiation at high levels of dose; furthermore, the model includes the square of dose in order to evaluate a carcinogenic process in which two events are necessary for cell initiation. At ORNL, however, occupational exposures to external radiation rarely occurred at dose rates which would suggest concern about cell-killing effects, and our analyses were not

focused on elucidating the effects of a multistage model. Consequently, we fitted models with a simple linear dose function which allowed easy interpretation of dose coefficients.

The additive relative risk and multiplicative relative risk models are used to describe the same tables of person-time and events, consequently their ability to describe the observed data may be compared quantitatively. The Aikaike information criterion (AIC), has been suggested for comparing the fit of different (non-nested) models to a dataset; this criterion imposes a penalty for increasing the number of parameters, as follows AIC= -2(maximum likelihood - number of parameters in model).[140]

Statistical Evaluation of Dose Weighting Functions

We relied on change in deviance statistics as a guide for evaluating the fit of dose terms in our regression models to the observed data.[136] The change in deviance values we report reflect the difference between the residual deviance in the full regression model and the residual deviance in the model in which one dose term has been dropped. These change in deviance statistics can be evaluated under a chi-squared distribution with one degree of freedom, providing a likelihood ratio test of the improvement in fit of the regression model upon inclusion of the dose term.

While the application of different weighting schemes is a common technique used in dose response analyses which evaluate lag assumptions, this method creates a problem for Poisson regression analyses which is seldom acknowledged.[92, 128] Since different ways of weighting cumulative dose lead to different tables of person-time and events, estimates of dose response associations derived from these tables cannot, formally, be compared using change in deviance statistics. However, the change in deviance upon exclusion of a dose term from the regression model does provide a quantitative indication of improvement in fit under different weighting functions. The larger the change in deviance, the better the dose term describes the observed mortality rates.[135]

Another method we used for evaluating the improvement in fit of a regression model when including separate terms for age-specific doses, was to compare two nested regression models. The table of person-time and events, which includes separate terms for the cumulative dose received before and after some critical age, may be thought of partitioning cumulative dose by age at exposure. We made the following comparison between nested statistical models (Figure 3.4):

Figure 3.4 Nested regression models of Age at Exposure Effects

Model 1: $\ln(\text{rate}) = ZB_z + B_1\,(\text{dose}<45) + B_2\,(\text{dose}>=45)$.
Model 2: $\ln(\text{rate}) = ZB + B_1\,(\text{dose}<45 + \text{dose}>=45)$.

Model 1 includes a vector of covariates as included in all models (Z) and their associated parameter estimates (B_z), as well as separate parameter estimates (B_1 and B_2) for cumulative dose received before and after age 45. Model 2 includes the same covariates, and a single parameter estimate (B_1) for the sum of the age-specific cumulative doses. Model 2 provides an estimate of the effects of lifetime cumulative dose, and is a nested form of Model 1. The difference in the residual deviances between the two models represents the change in deviance upon including the additional term for the separate of effects of doses received in two age periods, and provides a measure of the extent to which doses received in the two age periods have different effects.

Finally, we evaluated the fit of age-specific dose terms visually. Using the cell-specific mean doses associated with each cell of the person-time table, we created graphs of observed over expected cancer deaths by level of cumulative dose (see Appendix 1). These graphs allow evaluation of the fit of our regression models to the range of observed data.

Comments on Software for Regression Analyses

Regression analyses were conducted using the AMFIT program, which is part of the EPICURE software package.[136] In all analyses the convergence criterion was set to 10^{-5}, with forty iterations.

Chapter Four - Assessment of Study Variables in the Expanded Cohort

Overview

This chapter first describes the completeness of vital status follow-up and retrieval of death certificates for the expanded cohort of ORNL workers, and then presents an assessment of the distribution of person-time and cancer deaths by study covariates. These analyses were conducted in order to inform our decisions about how to categorize study variables, as well as to develop an understanding of differences in cancer mortality rates between groups within the study population.

In order to calculate stable regression estimates, variables were constructed so that at least one event was observed for each level of a stratifying variable, and the reference level for categorical variables was assigned to a stratum with a substantial number of observed events.

Vital Status Follow-up and Death Certificate Retrieval

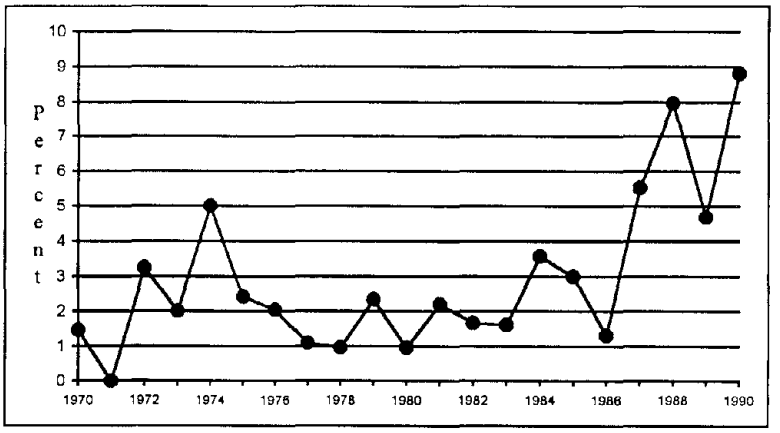
Vital status has been ascertained for 94% of the expanded cohort in follow-up through 1990 (Table 4.1). Searches failed to identify the vital status for 13% of the women and 3.9% of the men.

Table 4.1 Vital Status for the expanded cohort as of December 31, 1990

	Men (Percent) Number	Women (Percent) Number	Total (Percent) Number
Alive	(69.1) 7399	(75.8) 2568	(70.7) 9967
Dead	(27.0) 2890	(11.2) 379	(23.2) 3269
Unknown	(3.9) 417	(13.0) 442	(6.1) 859

Death certificates were retrieved for 97% of the decedents; however, there is evidence that retrieval of death certificates was not as complete in the last years of follow-up. The percentage of deaths without death certificates increases in the last four years of follow up (Fig. 4.1). Fewer states may have been contacted at the end of follow-up in the search to retrieve death certificates.

Figure 4.1 Percent of Deaths Without Death certificates by Calendar Year



Age at risk

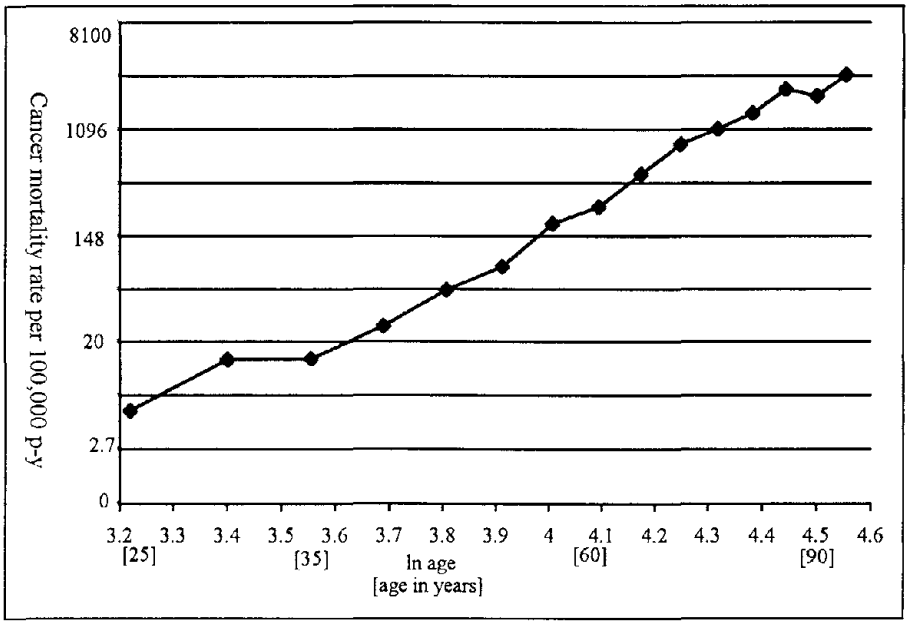
Age at risk was a time-dependent variable classified in five year intervals, from under 25 years to ninety years and over. The appropriateness of this categorization was assessed by examining the distribution of person-years and events within each of the age groups (Table 4.2).

Table 4.2 Cancer Deaths and Person-Time by Age Group

Age Group	All Cancer Deaths	Person-Years
<25	1	18009.7
25-30	5	34683.0
30-35	7	47752.2
35-40	15	55263.6
40-45	31	57343.2
45-50	45	53838.8
50-55	89	47527.0
55-60	103	40017.7
60-65	151	31558.2
65-70	176	20903.7
70-75	122	10984.1
75-80	75	5034.4
80-85	44	1887.1
85-90	12	584.5
90+	3	98.7

In regression analyses, age was treated as a continuous variable centered at 55 years, in a log-log (Weibull) relationship with cancer causes of death.[141] The appropriateness of a Weibull regression model was evaluated visually be graphing ln(age) by ln(risk) for all cancer mortality (Fig. 4.2). A Weibull model has previously been compared to a regression model using indicators term for age categories, and shown to be an efficient method for modeling cancer mortality as a function of age at risk.[71]

Figure 4.2 Graph of Log-log relation of Age at risk to Total Cancer mortality rate



Weibull and Gompertz models for total cancer mortality were compared with reference to change in deviance. The change in deviance for the Weibull model was substantial (1444.86, 1 d.f), and larger than the change in deviance (1424.71, 1 d.f.) when using a Gompertz model. We concluded that age at risk can be well described in the expanded cohort using a continuous term under a Weibull model for all cancer mortality.

Gender

Since workers with missing information about gender were excluded from our analyses, all members of the expanded cohort had an indicator of gender (Table 4.3).

Table 4.3 Number of Workers, Person-Years, and Deaths by Gender

Gender	Frequency	(Percent)	Person-Years	All Cancer Deaths	Crude All Cancer Rate (/100,000 p-y)	Age-adj All Cancer Rate (/100,000 p-y)
M	10706	(76.0)	326,767	750	229	249
F	3389	(24.0)	98,718	129	131	185

Similar to patterns observed nationally,[142] cancer mortality rates were higher among men than among women, and this difference remained after adjustment for age (Table 4.3). In a simple regression model which included age at risk as a main effect, inclusion of a term for gender resulted in a substantial improvement in fit for the regression model (change in deviance = 10.17, 1 df). While only 129 cancer deaths occurred among women, there were adequate numbers to examine gender as a main effect; we concluded that consideration of gender is important to a description of cancer mortality rates in this cohort.

Race

Workers were assigned to the following racial categories on the employment files: White, Black, Other. Workers of unknown race were excluded from analyses. Only 158 workers were classified as a race other than White or Black, and only one cancer death occurred in this category (Table 4.4). Consequently, we assessed the difference between Caucasian and non-Caucasian workers.

Table 4.4 Number of Workers, and Deaths by Race

Race	Frequency	(Percent)	All Cancer Deaths	(Percent)
White	13024	(92.4)	819	(93.2)
Black	913	(6.5)	59	(6.7)
Other	158	(1.1)	1	(0.1)

The crude all cancer mortality rate was lower among Caucasian workers than among workers of other races (Table 4.5). After adjustment for age in a simple regression model which included age and race as main effects, this difference was found to be small (Beta=0.084, se=0.13; change in deviance=0.39, 1 d.f.).

Table 4.5 Number of Workers, Person-Years, and Deaths by Race

Race	Frequency	(Percent)	Person-Years	All Cancer Deaths	Crude All Cancer Rate (/100,000 p-y)	Age adj All Cancer Rate (/100,000 p-y)
Caucasian	13024	(92.4)	398,674	819	205.4	235
Other	1071	(7.6)	26,812	60	223.8	256

We concluded that there was not sufficient data to examine more than two race groups in this cohort, and that the difference in age-adjusted cancer mortality rates between race groups was small.

Facility of Employment

We included workers who worked at some time at a DOE facility other than ORNL. Crude all cancer mortality rates were comparable between workers employed only at ORNL and those employed at other facilities as well as ORNL (Table 4.6).

Table 4.6 Person-years and Events, and Rate by Number of Facilities employed

Facility	Person-Years	All Cancer Deaths	Crude All Cancer Rate (/100,000 p-y)	Age adj All Cancer Rate (/100,000 p-y)
ORNL only	334,318	693	207	237.5
Other facilities as well	91,168	186	204	230.8

Similarly, after adjustment for age, little difference in cancer mortality rates was observed between these groups of workers (change in deviance upon inclusion of the facility term=0, 1 d.f.). We concluded that differences in all cancer mortality rates between workers employed at one, or more than one, facility were not substantial.

Paycode

There were six different indications of paycode recorded in the dataset, and some workers had missing paycode information (Table 4.7). In order to simplify our evaluation of differences among workers in the effects of paycode, we classified workers into three paycode categories. Monthly- and Hourly-paid workers were categorized according to their recorded paycode. The small number of workers for whom paycode was either missing or recorded as E,O, or S (which were categories with no assigned definition and may reflect data abstraction or keypunch errors) were assigned to the largest paycode group (Weekly-paid).

Table 4.7 Recorded Paycodes

Paycode	Frequency	Percent
A - Monthly	4844	34.6
E	1	<0.1
H - Hourly	2221	15.8
O	7	<0.1
S	11	0.1
W - Weekly	6935	49.5

Frequency Missing = 76

Crude all cancer mortality rates were highest among hourly-paid workers, lowest among monthly-paid workers, and intermediate among the weekly-paid (Table 4.8).

Table 4.8 Number of Workers, Person-Years, and Deaths by Paycode

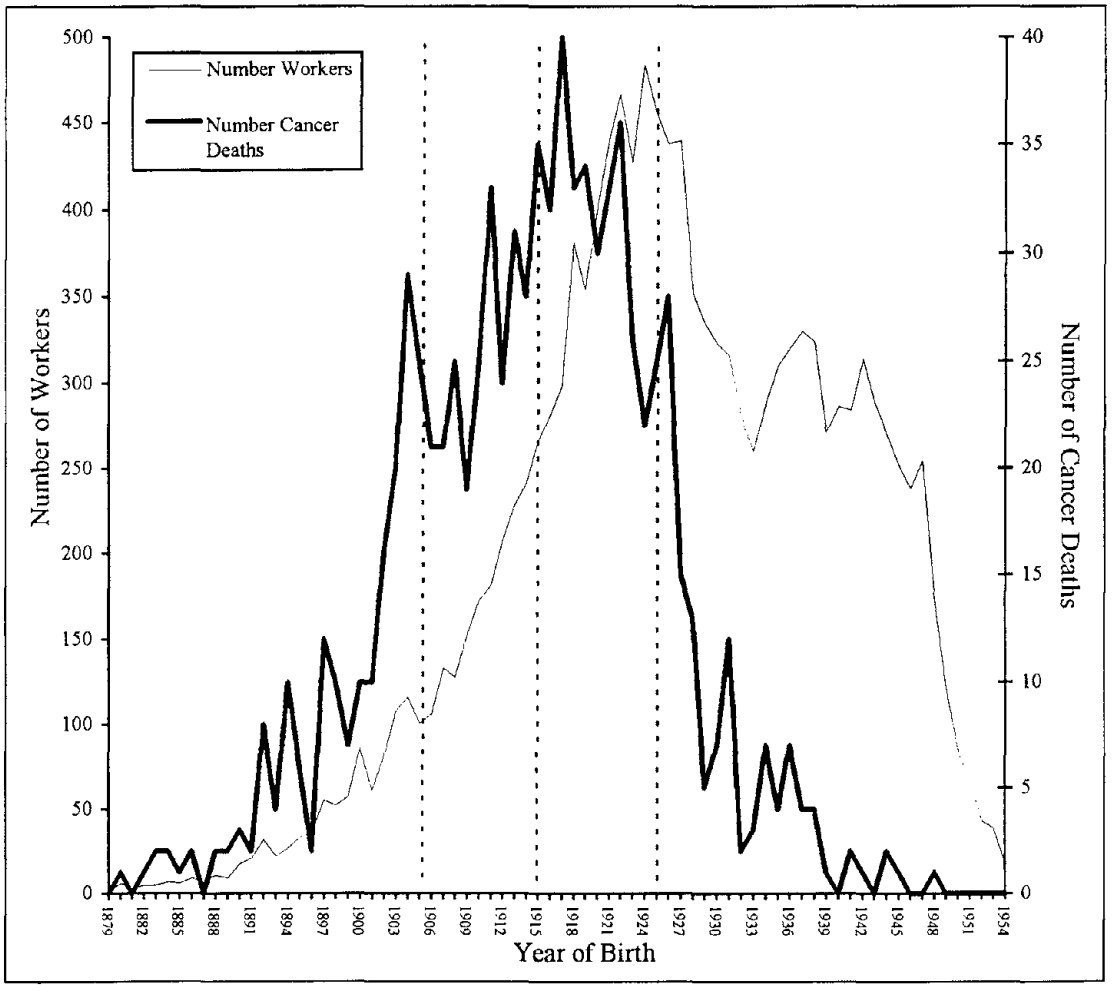
Paycode	Frequency (Percent)	Person-Years	All Cancer Deaths	Crude All Cancer Rate (/100,000 p-y)	Age adj All Cancer Rate (/100,000 p-y)
Weekly, or other	7030 (49.9)	214,684	442	205.8	251.6
Hourly	2221 (15.8)	65,706	181	275.4	297.0
Monthly	4844 (34.4)	145,096	256	176.4	188.7

Adjustment for age did not change the impact of paycode on cancer mortality rates. Monthly paid workers were estimated to have lower age-adjusted cancer mortality rates than weekly-paid workers (Beta=-0.287, se=0.079), and age-adjusted mortality rates were higher for hourly than weekly-paid workers (Beta=0.166, se=0.088). The change in deviance upon inclusion of indicator terms for paycode was substantial (24.46, 2 df). We concluded that paycode should be considered in three categories, and that the important distinction may be the lower cancer mortality rates among monthly-paid workers.

Birth Cohort

Based upon the distribution of all cancer deaths (Figure 4.2; Table 4.9), and upon the previous classification of birth cohort,[19] we decided to categorize workers into four birth cohorts.

Figure 4.3 Distribution of Workforce and Cancer Deaths by Year of Birth



While crude all cancer mortality rates differed substantially between birth cohorts (Table 4.9), this was largely due to differences in the age distribution of person-time between these groups.

Table 4.9 Number of Workers, Person-Years, and Deaths by Birth Cohort

Year of Birth	Frequency	(Percent)	Person-Years	All Cancer Deaths	Crude All Cancer rate (/100,000 p-y)	Age Adjusted All Cancer rate (/100,000 p-y)
<1905	874	(6.2)	22,902	162	706.9	241.08
1905-15	1650	(11.7)	55,968	252	450.0	258.3
1915-25	3798	(26.9)	139,233	321	230.4	245.2
1925+	7773	(55.2)	207,383	144	69.4	207.9

Adjustment for age in a simple model which included age at risk and birth cohort as main effects suggests that differences in age adjusted cancer mortality rates between birth cohorts are small (change dev= 3.4, 3 df). Examination of age-specific cancer mortality rates for each birth cohort provides further information about cancer mortality rates across birth cohorts (Table 4.10).

Table 4.10 Age-specific cancer mortality rates (per 100,000 p-y) by birth cohort

	Born <1905 Rate (# deaths)	Born 1905-15 Rate (# deaths)	Born 1915-25 Rate (# deaths)	Born >=1925 Rate (# deaths)
Age 55-60	223.2 (8)	198.1 (14)	311.7 (52)	228.7 (29)
Age 65-70	1013.3 (32)	819.58 (48)	811.6 (95)	544.0 (1)
Age 75-80	1308.9 (25)	1640.6 (50)	0 (0)	0 (0)

The 1925+ birth cohort, for which deaths could not yet have occurred among persons at the oldest ages, appears to have the lowest age-adjusted cancer mortality rate (Table 4.9); however, differences in rates between birth cohorts are small when considering the standard errors for the age-adjusted estimates of the birth cohort effects (Table 4.11).

Table 4.11 Age- and Birth Cohort- adjusted cancer mortality rates

Parameter		Beta	se
Intercept		5.502	0.059
ln(age)		5.397	0.215
Birth Cohort(2)	[1905-1915]	0.052	0.087
Birth Cohort(3)	[<1905]	-0.017	0.104
Birth Cohort(4)	[>=1925]	-0.165	0.107

model: ln(rate)=ln(age)+cohort

Employment Status

While crude all cancer mortality rates differed between actively employed and terminated workers, this was largely due to differences in the age distribution of person-time between categories of employment status (Table 4.12). Upon inclusion of employment status in a simple model that included age, the change in deviance was 1.53 (1 df). However, our interest in this factor is primarily in its relationship in interaction with age at risk.[110]

Table 4.12 Person-years and Events by Active Work Status

Employment Status	Person-Years	All Cancer Deaths	Crude All Cancer rate (/100,000 p-y)	Age Adjusted All Cancer rate (/100,000 p-y)
Not active	255670	717	280.34	243.7
Active	169816	162	95.39	217.4

Internal Radiation Monitoring

There were not substantial differences in cancer mortality between workers by status of internal monitoring (lagged ten years) after adjustment for age (change in deviance upon including internal monitoring status=0.64, 2 d.f). While cancer deaths were observed for each category of internal monitoring status, only ten deaths occurred among those not eligible to be monitored (Table 4.13).

Table 4.13 Person-Years and Events by Internal Monitoring Status Lagged 10 yr.

Internal Monit Status	Person-Years	All Cancer Deaths	Crude All Cancer rate (/100,000 p-y)	Age Adjusted All Cancer rate (/100,000 p-y)
Not monitored	306,384	589	192.3	239.4
Monitored	95,659.4	280	292.8	227.2
Not Eligible	23,442.5	10	42.65	263.5

Categorization of Study Variables in Person-time Tables

Age at risk -

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
<25	25<= <30	30<= <35	35<= <40	40<= <45	45<= <50	50<= <55	55<= <60	60<= <65	65<= <70	70<= <75	75<= <80	80<= <85	85<= <90	>=90

Birth Cohort -

1	2	3	4
1915 <= yob < 1925	1905 <= yob < 1915	yob < 1905	1925 <= yob

Employment Status-

1	2
No longer working	actively employed

External Radiation Dose - in mSv

1	2	3	4	5	6	7	8
0	0 < 20	20 < 40	40 < 60	60 < 80	80 < 100	100 < 120	>= 120

Facility -

1	2
Employed at X10 only	Employed at more than one facility

Gender -

1	2
Male	Female

Internal Monitoring Status-

1	2	3
Not Monitored	Monitored	Not Eligible (Year of obs < 1951)

Paycode -

1	2	3
Weekly-paid or Other	Hourly-paid	Monthly-paid

Race -

1	2
Caucasian	Not Caucasian

Chapter Five - Regression Model Development for the Expanded Cohort

Overview

This chapter presents bivariate analyses of the study covariates, and describes the development of a regression model for the expanded cohort. Development of a regression model could not proceed by simply assessing the effect of interaction and main effect terms on our dose response estimates, since we were interested in the effects of doses received in different periods of exposure (defined by age and latency), which lead to different distributions of dose. Consequently, our approach was to develop a regression model which would describe mortality rates using the available covariates, and use this model to control for confounding when assessing different dose response relationships. While our primary interest was in analyses of all cancer mortality, we attempted to develop a model which could be used for analyses of the association between radiation and specific cancer and non-cancer causes of death.

To develop this model, we began by examining the distribution of cancer deaths by cross-classification of covariates. Stratified analyses revealed that some interactions between covariates could not be examined because they involved few, or no, cancer deaths. We examined differences in crude and age-adjusted cancer rates within strata of cross-classified covariates as an initial method to identify interactions of interest. Interactions of interest were included in a regression model, and, by step-wise elimination, we evaluated the contribution of these interaction terms to our regression model.

Analyses examined the following:

Cross-tabulations of age with-

- gender
- race
- pay
- internal
- cohort
- work

Cross-tabulations of gender with-

- race
- pay
- internal
- cohort
- work

Cross-tabulations of race with-

- pay
- internal
- cohort
- work

Cross-tabulations of paycode with-

- internal
- cohort
- work

Cross-tabulations of internal with-

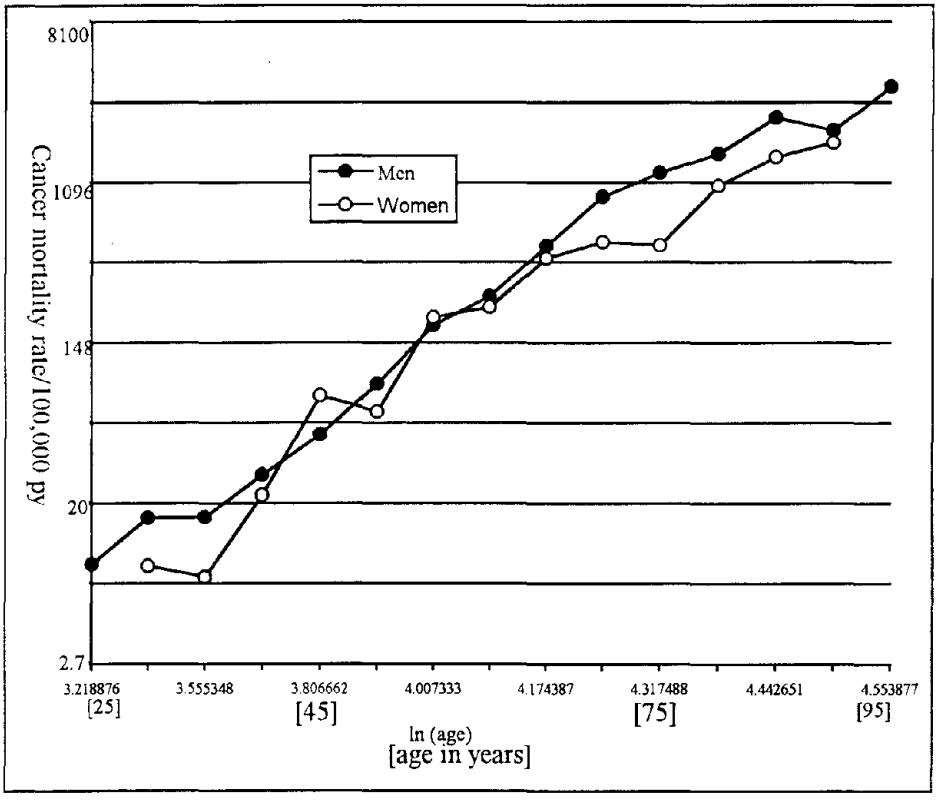
- cohort
- work

Cross-tabulations of cohort with work

Interaction of Gender with Age

We considered whether age-specific mortality rates were similar, on a relative risk scale, for men and women. We examined age-specific mortality rates by gender (Figure 5.1); we then evaluated the interaction between age and gender using a regression model. This model included main effects for age (using a Weibull model) and gender, and an interaction term between the two. Inclusion of the interaction term was associated with a change in deviance of 4.07 (1 d.f.); the parameter estimate for this interaction term was -0.926 (se=0.450). The results suggest that the slope of the Weibull model for women may not be as steep as that for men. While it appears appropriate to model the increase in cancer rates on a ln-ln scale with age, the interaction term suggests a difference in this model by gender.

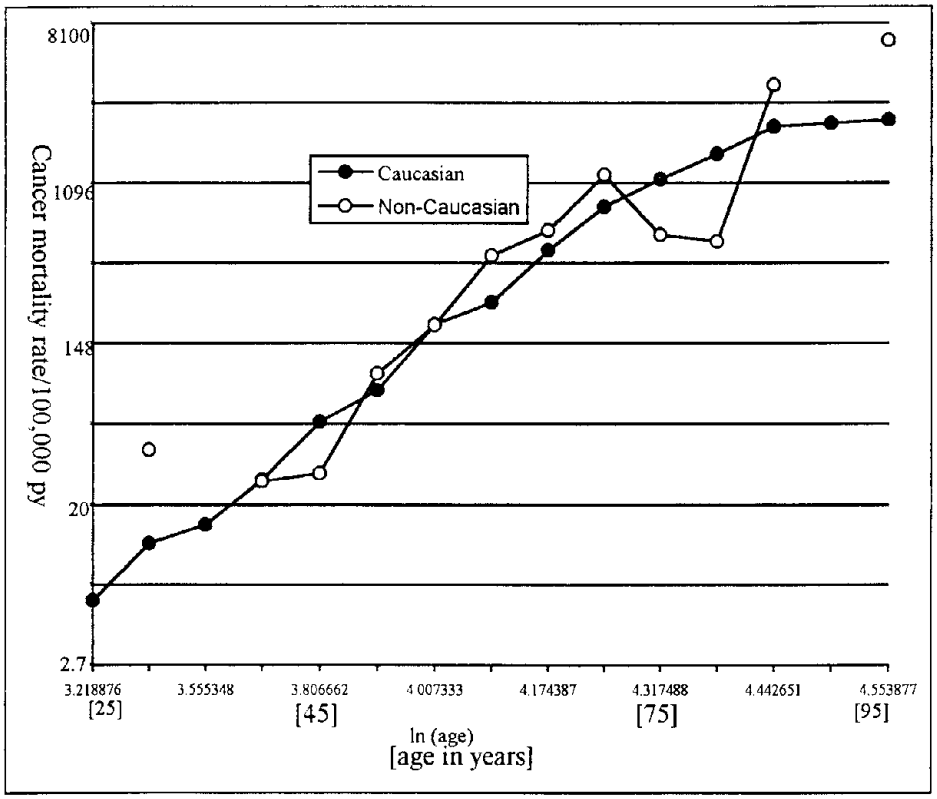
Figure 5.1 Age-specific Total Cancer Rates by Gender



Interaction of Race with Age

Similarly, we considered whether the effect of race was constant on relative risk scale with age (Figure 5.2). Using a regression model which included main effects for age and race, and an interaction term between the two, resulted in a change in deviance of 0.93 (1 d.f.) upon inclusion of this interaction term; the parameter estimate for the interaction term was -0.614 (se=0.628). The small change in deviance suggests that an interaction term does not substantially add to the regression model; in part this may reflect the lack of data for non-Caucasian workers. The small number of non-Caucasian workers in this cohort is evident by the lack of data upon which to estimate cancer mortality rates for some age groups (Figure 5.2).

Figure 5.2 Age-Specific Total Cancer Rates By Race



Interaction of Paycode with Age

To examine whether age-specific mortality rates differed between the three paycode categories, we used a regression model including age and paycode as main effects, and an interaction between the age at risk and paycode (Table 5.1). A small change in deviance upon inclusion of these interaction terms (1.25, 2 df) suggests that there is little modification of age-specific mortality rates by paycode, when considered on a multiplicative scale.

Table 5.1 Interaction between Paycode and Age

Parameter		Beta	se
Intercept		5.55	0.06
Pay(2)	[Hourly-paid]	0.12	0.11
Pay(3)	[Monthly-paid]	-0.34	0.09
lnage		5.39	0.23
ln(age)*Pay(2)	[Age*Hourly-paid]	0.34	0.47
ln(age)*Pay(3)	[Age*Monthly-paid]	0.42	0.41

model: ln(rate)=ln(age)+paycode+ln(age)*paycode

Interaction of Internal Monitoring with Age

We evaluated the difference in age-specific mortality rates by internal monitoring status using a regression model including age and internal monitoring status as main effects, and an interaction between the two terms. Examination of the parameter estimates for the interaction terms suggests that age-specific rates may differ by internal monitoring status, particularly among those workers not eligible to be monitored. However, only ten cancer deaths occurred among the group of workers not eligible for internal monitoring (Table 4.13), so a difference in age-specific cancer mortality rates for this group is difficult to assess. The change in deviance upon inclusion of these interaction terms was 5.05 (2 df).

Table 5.2 Interaction between Internal and Age

Parameter		Beta	se
Intercept		5.48	0.05
ln(age)		5.53	0.20
Internal(2)	[Not Monitored]	-0.11	0.09
Internal(3)	[Not Eligible]	-0.45	0.48
ln(age)*Internal(2)	[Age*Not Monitored]	0.40	0.42
ln(age)*Internal(3)	[Age*Not Eligible]	-2.44	1.21

model: ln(rate)=ln(age)+internal+ln(age)*internal

Interaction of Birth Cohort with Age

We evaluated the difference in age-specific mortality rates by birth cohort using a regression model which included age and birth cohort as main effects, and interactions between these terms (Table 5.3). The small change in deviance upon inclusion of these interaction terms (change deviance with inclusion of interaction term =1.2, 3 df) suggests that there is little modification on a multiplicative scale.

Table 5.3 Interaction between Birth Cohort and Age

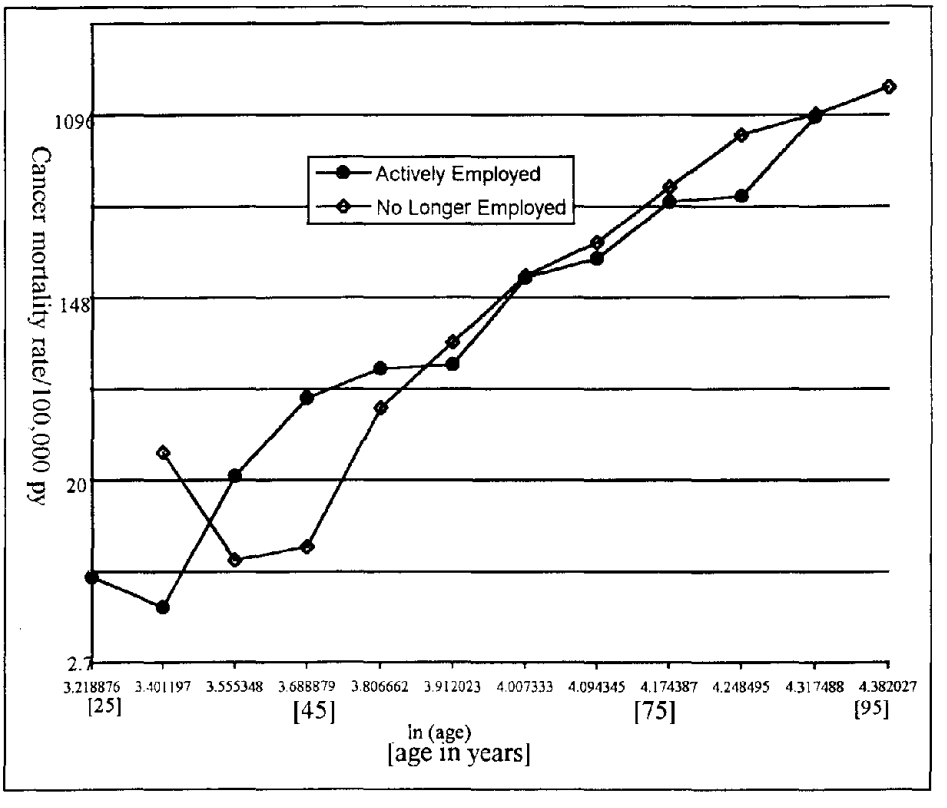
Parameter		Beta	se
Intercept		5.50	0.06
ln(age)		5.42	0.36
Cohort(2)	[1905-1915]	-0.01	0.12
Cohort(3)	[<1905]	0.06	0.17
Cohort(4)	[>=1925]	-0.18	0.11
ln(age)*Cohort(2)	[Age*1905-1915]	0.31	0.55
ln(age)*Cohort(3)	[Age*<1905]	-0.30	0.63
ln(age)*Cohort(4)	[Age*>=1925]	-0.25	0.59

model: ln(rate)=ln(age)+cohort+ln(age)*cohort

Interaction of Employment Status with Age

Previous analyses of the ORNL cohort have considered an interaction between the effects of employment status and age at risk. As discussed in Chapter 2, the difference in health status between employed and terminated workers has been observed to change with older ages in many cohorts. This may be because workers who remain employed at older ages are healthier than those who leave the workforce at older ages, while at younger ages terminating employment may be less often an indicator of poor health (and more often a reflection of job changes). Age-specific cancer mortality rates appear to follow this pattern in the ORNL cohort; at younger ages mortality rates tend to be higher among the actively employed, while at older ages mortality rates tend to be lower among the actively employed (Figure 5.3).

Figure 5.3 All Cancer Rates by Age group and Employment Status (2-yr. lag)



We constructed a regression model which included age and employment status; the change in deviance upon inclusion of employment status-lnage interaction term was 6.4, 1 d.f. (Table 5.4).

Table 5.4 Interaction between Employment Status and Age

Parameter		Beta	se
Intercept		5.46	0.05
ln(age)		5.71	0.21
Work(2)	[Actively Employed]	-0.12	0.096
ln(age)*Work(2)	[Age*Actively Employed]	-1.20	0.46

Interaction of Gender with Race

There is a limited amount of data with which to assess an interaction between race and gender (Table 5.5). However, in our univariate analyses (Tables 4.2 and 4.4) we noted that men had higher cancer mortality rates than women, and that nonwhites had higher cancer mortality rates than whites. In bivariate analyses these associations are complicated by an interaction between race and gender (Table 5.5). Nonwhite women had the highest cancer rates. Nonwhite males had lower rates than white males. The main effect for women (lower rates than men) appears to be due to the rates for white women; and, the main effect for race (higher rates for nonwhites than for whites) appears to be due to the higher rates among nonwhite women. This interaction persisted in age-adjusted analyses. In a model which included race, gender, and age as main effects, and an interaction between race and gender, a substantial change in deviance was observed upon inclusion of this interaction term (change in deviance with inclusion of interaction= 4.74, 1 d.f.; parameter estimate for the interaction term which represented non-white women= 0.71, se=0.31).

Table 5.5 Person-years, Deaths, Crude and Age-adjusted Cancer Rates by Race and Gender

	Person-Years	All Cancer Deaths	Crude All Cancer Rate (/100,000 p-y)	Age-adj All Cancer Rate (/100,000 p-y)
White males	306,880	706	230.0	249.6
White females	91,793	113	123.1	174.4
non-White males	19,887	44	221.2	165.2
non-White females	6,925	16	231.0	334.5

Interaction of Paycode with Gender

Crude cancer mortality rates were similar for men and women among monthly-paid workers (Table 5.6, column 3); however, among weekly-paid workers (where the most person-time and deaths were observed) crude cancer mortality rates for women were at their lowest, while among weekly-paid men crude cancer mortality rates were higher than for monthly-paid men.

Table 5.6 All Cancer Deaths and Crude All Cancer Rates by Gender and Paycode

	Weekly-Paid All Cancer Rates (Deaths)	Hourly-Paid All Cancer Rates (Deaths)	Monthly-Paid All Cancer Rates (Deaths)
males	258.7 (341)	284.25 (171)	176.6 (238)
females	121.87 (101)	180.31 (10)	174.8 (18)
Ratio	2.12	1.57	1.01

After adjustment for age at risk, the difference in cancer mortality rates by paycode and gender were not substantial (change in deviance with inclusion of interaction= 2.0, 2 d.f.). As noted earlier, the effects of gender appeared to differ by race; consequently, we further examined differences in the effects of paycode when simultaneously considering race and gender (see Table 5.11).

Table 5.7 Age-Adjusted All Cancer Mortality Rates by Gender and Paycode

Parameter		Beta	se
Intercept	[Men, Weekly-Paid]	5.65	0.06
ln(age)		5.51	0.17
Gender(2)	[Women, Weekly-Paid]	-0.43	0.11
Pay(2)	[Men, Hourly-Paid]	0.077	0.09
Pay(3)	[Men, Monthly-Paid]	-0.40	0.08
Gender(2)*Pay(2)	[Women, Hourly-Paid]	0.01	0.34
Gender(2)*Pay(3)	[Women, Monthly-Paid]	0.39	0.27

model: rate= ln(age)+pay+gender+pay*gender

Interaction of Internal Monitoring with Gender

We evaluated differences in the effects of internal monitoring status among men and women; however, there were no deaths observed among women not eligible to be monitored (Table 5.8). Consequently, a regression model which included an interaction between gender and internal monitoring status had problems with convergence because of the lack of deaths among women not eligible for internal monitoring (change in deviance was 3.89, 2 d.f.)

Table 5.8 Crude Cancer Mortality Rate and Cancer Deaths by Gender and Internal Monitoring Status

	Not monitored All Cancer Rate per 100,000 p-y (Deaths)	Monitored All Cancer Rate per 100,000 p-y (Deaths)	Not Eligible All Cancer Rate per 100,000 p-y (Deaths)
males	211.8 (479)	316.4 (261)	55.1 (10)
females	137.1 (110)	144.2 (19)	-- (0)

Interaction of Birth Cohort with Gender

As demonstrated in univariate analyses, an examination of differences in cancer mortality rates by birth cohort must account for confounding by age at risk. Using an age adjusted model (Table 5.9), important differences were observed in birth cohort specific cancer mortality rates by gender (change in deviance with inclusion of interaction terms=12.64, 3 df).

Table 5.9 Age-adjusted All Cancer Mortality Rates by Gender and Birth Cohort

Parameter		Beta	se
Intercept	[Men, 1915-25]	5.527	.06542
Gender(2)	[Women, 1915-25]	-.1281	.1389
Cohort (2)	[Men, 1905-15]	.1101	.09318
Cohort (3)	[Men, <1905]	.01849	.1090
Cohort (4)	[Men, 1925+]	-.2039	.1205
Gender(2)*Cohort (2)	[Women, 1905-15]	-.6725	.2761
Gender(2)*Cohort (3)	[Women, <1905]	-.6899	.3702
Gender(2)*Cohort (4)	[Women, 1925+]	.1968	.2373
ln(age)		5.427	.2152

model: ln(rate)=ln(age)+gender+cohort+gender*cohort

Interaction of Active Employment Status with Gender

Evaluation of differences in the effects of employment status by gender should further consider the interaction between age at risk and employment status (as described earlier). This requires examination of a three-way interaction. In order to assess this interaction, we created a new indicator variable 'genderwork' which included four levels (representing the combination of the two levels of the gender variable and the two levels of the employment status variable). It should be noted that there is little data for women with which to assess differences in age-specific cancer rates by employment status (Table 5.10).

Table 5.10 Cancer Deaths by Gender and Employment Status

	No Longer Employed	Actively Employed
Male	600	150
Female	117	12

To assess this modification we compared two regression models. The first was a model that included age, gender, and employment status as main effects, and an interaction between employment status and age. The second model included age and the 'genderwork' term as main effects (although the genderwork term includes four levels thereby allowing differences in employment status by gender), and an interaction between 'genderwork' and age. The difference in deviance between the two models is 8.0, 3 d.f.

model: ln(rate)=ln(age)+work+gender+ln(age)*work

Residual Deviance = 2336.1, 8323 d.f.

model: ln(rate)=ln(age)+genderwork+ln(age)*genderwork

Residual Deviance = 2328.1, 8320 d.f.

However, this change in deviance also reflects, in part, the consequence of controlling for the two-way interaction between age and gender. We evaluated the effect of including the three-way interaction in a model which already included an age-gender interaction. The model with an age-gender interaction, then, was compared to the model with a three-way age-gender-work interaction. The inclusion of the three-way interaction leads to a change in deviance of 4.2 (2 d.f.).

model: ln(rate)=ln(age)+work+gender+ln(age)*work+ln(age)*gender
Residual Deviance = 2332.3 , 8322 d.f.

model: ln(rate)=ln(age)+genderwork+ln(age)*genderwork
Residual Deviance = 2328.1, 8320 d.f.

Interaction of Paycode with Race

As we described above, racial differences in cancer mortality rates appear to differ by gender; consequently, we present tabulations of person-time and events stratified by race and gender, as well as paycode. However, in this cohort differences in mortality rates by race and paycode cannot be evaluated with any certainty, whether or not one stratifies by gender (Table 5.11). Only one cancer death occurred among nonwhites in the monthly paycode group, and no deaths occurred among non-white women paid monthly.

Table 5.11 Cancer Deaths by Race, Gender and Paycode

	Weekly All Cancer	Hourly All Cancer	Monthly All Cancer
White males	311	158	237
White females	88	7	18
non-White males	30	13	1
non-White females	13	3	0

Interaction of Internal Monitoring with Race

Similarly, examination of differences in cancer mortality rates by internal monitoring status and race was limited by the small number of cancer deaths. Only 5 cancer death were observed among all nonwhite workers who were not monitored for internal deposition of radionuclides (Table 5.12).

Table 5.12 Cancer Deaths by Race, Gender and Internal Monitoring Status

	Not monitored All Cancer	Monitored All Cancer	Not Eligible All Cancer
White males	111	250	345
White females	23	14	76
non-White males	2	11	31
non-White females	3	5	8

Evaluation of the interaction between internal monitoring and race, in a model which includes age, race, and internal monitoring as main effects, suggests there is little difference in the effects of internal monitoring by race (change in deviance=2.2, 2 d.f.).

Interaction of Birth Cohort with Race

We evaluated whether birth cohort effects differed by race, using a regression model which included age, birth cohort, and race as main effects; the inclusion of birth cohort-race interaction was associated with a small change in deviance (change dev=3.8, 3 df). Evaluation of differences due to a race-gender interaction were not evaluated, given the limited number of cancer deaths distributed by race, gender and birth cohort (Table 5.13).

Table 5.13 Cancer Deaths by Race, Gender, and Birth cohort

	1915-25 All Cancer	1905-15 All Cancer	<1905 All Cancer	1925+ All Cancer
White males	236	226	142	192
White females	62	13	5	33
non-White males	20	7	11	6
non-White females	3	6	4	3

Interaction of Employment Status with Race

Evaluation of differences in the effects of employment status by race requires considering the interaction between age at risk and employment status (as described earlier). In order to assess this three-way interaction, we created a new indicator variable 'racework' which included four levels (representing the combination of the two levels of the race variable and the two levels of the employment status variable). It should be noted that there are few cancer deaths among nonwhites with which to assess differences in age-specific cancer rates by employment status (Table 5.14).

Table 5.14 Cancer Deaths by Race, Gender, and Employment Status

	No Longer Employed	Actively Employed
White males	566	140
White females	105	8
non-White males	34	10
non-White females	12	4

To assess this modification we compared two regression models. The first was a model that included age, race, and employment status as main effects, and an interaction between employment status and age. The second model included age and the 'racework' term as main effects (although the racework term includes four levels thereby allowing differences in employment status by race), and an interaction between 'racework' and age. We did not include the other two-way interaction (race with age), since we were not planing on including this interaction in our final model and are more interested in assessing the overall effect of including the 3-way interaction in the final model. The difference in residual deviances was 3.1 (3 d.f.).

model: ln(rate)=ln(age)+work+race+ln(age)*work

Residual Deviance = 2346.6, 8323 d.f.

model: ln(rate)=ln(age)+racework+ln(age)*racework

Residual Deviance = 2343.5, 8320 d.f.

Interaction of Internal Monitoring with Paycode

We examined the distribution of all cancer deaths by paycode and internal monitoring status (Table 5.15).

Table 5.15 Cancer Deaths by Paycode by Internal

	Weekly-Paid	Hourly-Paid	Monthly-Paid
Not Monitored	330	80	179
Monitored	105	100	75
Not Eligible	7	1	2

Using a simple regression model which included age, paycode and internal monitoring status, we evaluated the interaction of paycode with internal monitoring status. The interaction was associated with a change in deviance of 1.8 (4 df).

Interaction of Birth Cohort with Paycode

Previous analyses of this cohort have included an interaction between paycode and birth cohort. This interaction has been attributed to temporal changes in the association between socioeconomic factors and cause-specific mortality. We evaluated the age-adjusted difference in paycode effects between cohorts (Table 5.16). The most important distinction is between monthly and nonmonthly workers. For all cancer mortality, inclusion of the interaction between paycode and birth cohort did not contribute much to the fit of the regression model (change in deviance with inclusion of interaction terms= 6.79 , 6 df).

Table 5.16 Age-Adjusted Paycode-Birth Cohort Interaction

Parameter		Beta	se
1		5.62	0.08
Pay (2)	[Hourly]	0.14	0.14
Pay (3)	[Monthly]	-0.42	0.13
Cohort (2)	[1905-1915]	-0.07	0.13
Cohort (3)	[<1905]	-0.17	0.14
Cohort (4)	[>=1925]	-0.11	0.15
Pay(2)* Cohort(2)	[Hourly*1905-15]	0.04	0.22
Pay(2)* Cohort(3)	[Hourly*<1905]	0.09	0.27
Pay(2)* Cohort(4)	[Hourly*>=1925]	-0.06	0.26
Pay(3)* Cohort(2)	[Monthly*1905-15]	0.31	0.19
Pay(3)* Cohort(3)	[Monthly*<1905]	0.38	0 .23
Pay(3)* Cohort(4)	[Monthly*>=1925]	-0.17	0.24
ln(age)		5.44	0.22

model: ln(rate)=ln(age)+cohort+pay+pay*cohort

Interaction of Employment Status with Paycode

Evaluation of differences in the effects of employment status by paycode requires considering the interaction between age at risk and employment status (Table 5.17). In order to assess this three-way interaction, we created a new indicator variable 'paywork' which included six levels (representing the combination of the three levels of the pay variable and the two levels of the employment status variable).

Table 5.17 Cancer Deaths by Race, Gender and Employment Status

	No Longer Working	Actively Employed
Weekly-Paid	377	65
Hourly-Paid	128	53
Monthly-Paid	212	44

To assess this modification we compared two regression models. The first was a model that included age, paycode, and employment status as main effects, and an interaction between employment status and age. The second model included age and the 'paywork' term as main effects (although the paywork term includes six levels thereby allowing differences in employment status by paycode), and an interaction between 'paywork' and age. The difference in residual deviances was 6.0 (6 d.f.).

model: ln(rate)=ln(age)+work+pay+ln(age)*work

Residual Deviance = 2321.1, 8322 d.f.

model: ln(rate)=ln(age)+paywork+ln(age)*paywork

Residual Deviance = 2315.1, 8316 d.f.

Interaction of Birth Cohort with Internal Monitoring

We had a limited ability to evaluate potential differences in the association between internal monitoring status and all cancer mortality between birth cohorts (Table 5.18). Until 1951, no worker was monitored for internal radionuclide exposure; consequently, for workers in the first two birth cohorts, nearly all the person-time is classified as not eligible for internal monitoring. Similarly, with later birth cohorts, the proportion of person-time and cases classified as not eligible for internal monitoring declines.

Table 5.18 Cancer Deaths by Birth Cohort and Internal Monitoring

	Born <1905	Born 1905-15	Born 1915-25	Born 1925+
Not monitored	130	164	209	86
Monitored	28	85	109	58
Not Eligible	4	3	3	0

There are no deaths observed in the most recent birth cohort among those not eligible for internal monitoring; consequently, there is a lack of convergence when this interaction is included in a regression model.

Among those categories where there were data, we might expect that the association between birth cohorts and internal monitoring status would differ. Few workers from the early birth cohorts remained employed long enough to become eligible for internal monitoring. Consequently, those workers born in the earlier birth cohorts who remained employed long enough to be eligible for internal monitoring, had remained employed until older ages. As we noted above, workers actively employed at older ages had lower cancer mortality rates than terminated workers in this cohort. This effect should be addressed in part by controlling for employment status in our final model.

Interaction of Employment Status with Internal Monitoring

Evaluation of differences in the effects of employment status by internal monitoring, requires considering the interaction between age at risk and employment status (Table 5.19). In order to assess this three-way interaction, we created a new indicator variable 'intwork' which included six levels (representing the combination of the three levels of the internal variable and the two levels of the employment status variable).

Table 5.19 Cancer Deaths by Race, Gender, and Employment Status

	No Longer Employed	Actively Employed
Not Monitored	521	68
Monitored	193	87
Not Eligible	3	7

To assess this modification we compared two regression models. The first was a model that included age, internal, and employment status as main effects, and an interaction between employment status and age. The second model included age and the 'internalwork' term as main effects (although the internalwork term includes six levels thereby allowing differences in employment status by internal), and an interaction between 'internalwork' and age. The difference in residual deviances was 4.4 (6 d.f.).

model: ln(rate)=ln(age)+work+internal+ln(age)*work

Residual Deviance = 2346.9, 8322 d.f.

model: ln(rate)=ln(age)+internalwork+ln(age)*internalwork

Residual Deviance = 2342.5, 8316 d.f.

Interaction of Employment Status with Birth Cohort

Evaluation of differences in the effects of employment status by cohort, requires considering the interaction between age at risk and employment status (as described earlier). This requires consideration of a three-way interaction (Table 5.20). In order to assess this interaction, we created a new indicator variable 'cohortwork' which included eight levels (representing the combination of the four levels of the cohort variable and the two levels of the employment status variable).

Table 5.20 Cancer Deaths by Birth Cohort and Employment Status

	No Longer Employed	Actively Employed
Born 1915-1925	252	69
Born 1905-1915	219	33
Born <1905	147	15
Born 1925+	99	45

To assess this modification we compared two regression models. The first was a model that included age, cohort, and employment status as main effects, and an interaction between employment status and age. The second model included age and the 'cohortwork' term as main effects (although the cohortwork term includes eight levels thereby allowing differences in employment status by cohort), and an interaction between 'cohortwork' and age. The difference in residual deviances was 7.1 (9 d.f.).

model: ln(rate)=ln(age)+work+cohort+ln(age)*work

Residual Deviance = 2343.6, 8321 d.f.

model: ln(rate)=ln(age)+cohortwork+ln(age)*cohortwork

Residual Deviance = 2336.52, 8312 d.f.

Table 5.21 Summary of Evaluation of Interactions Between Covariates

Terms		Change in deviance (d.f.)	Interaction of Interest
Interactions with age-	gender	4.1 (1)	X
	race	0.9 (1)	
	pay	1.3 (2)	
	internal	5.1 (2)	
	cohort	1.2 (3)	
	work	6.4 (1)	X
Interactions with gender[†]-	race	4.7 (1)	X
	pay	2.0 (2)	
	internal	not evaluated-sparse #'s	
	cohort	12.6 (3)	X
	work[‡]	4.2 (2)	
Interactions with race[†]-	pay	not evaluated-sparse #'s	
	internal	2.2 (2)	
	cohort	3.8 (3)	
	work	3.1 (3)	
Interactions with pay[†]-	internal	1.8 (4)	
	cohort	6.8 (6)	X
	work	6.0 (6)	
Interactions with internal[†]-	cohort	not evaluated-sparse #'s	
	work	4.4 (6)	
Interactions with cohort[†]-	work	7.1 (9)	

[†] age-adjusted

[‡] adjusted for age*gender interaction

Stepwise Model Development

We evaluated the following five interactions, suggested by the stratified analyses and by previous research, using stepwise elimination from a regression model:[82, 110, 114, 143]

(1) Age specific cancer rates differ by gender
(2) Age specific cancer rates differ by employment status
(3) Socioeconomic inequalities in mortality differ between birth cohorts
(4) Race effects modified by gender
(5) Birth cohort effects differ by gender

Our approach to this model building was to develop a regression model for all cancer mortality in this cohort which would allow us to consider cumulative dose under different weighting strategies. Consequently, our evaluation of the stepwise elimination of an interaction term was not made with reference to the effect on some radiation-cancer association. Rather, we entered all main effects and interactions, and then examined the magnitude of the associated parameter estimates for the interaction terms (Figures 5.4, 5.5) and the change in deviance for the regression model upon dropping the interaction terms (Figure 5.6).

Figure 5.4 Parameter Estimates for Regression model

Name	Parameter Estimate	Std.Err.	Score
%CON	5.825	.1074	-.480E-10
LNMAGE	5.697	.2873	.257E-10
RACE_2	-.1685	.1570	-.731E-11
GENDER_2	-.4015	.1619	-.474E-11
PAY_2	.09596	.1510	-.665E-11
PAY_3	-.5525	.1387	-.100E-10
COHORT_2	-.07868	.1416	-.167E-10
COHORT_3	-.3111	.1555	-.424E-10
COHORT_4	-.1674	.1783	-.601E-12
WORK_2	-.1549	.1031	-.338E-10
INTERNAL_2	-.08358	.08220	.358E-15
INTERNAL_3	.04311	.3378	-.151E-09
FACIL_2	-.1192	.08564	-.653E-11
RACE_2 * GENDER_2	.9036	.3122	-.247E-11
COHORT_2 * GENDER_2	-.5772	.2951	-.226E-11
COHORT_3 * GENDER_2	-.5173	.3964	-.344E-11
COHORT_4 * GENDER_2	.1985	.2771	-.428E-12
PAY_2 * COHORT_2	-.01022	.2234	-.315E-11
PAY_2 * COHORT_3	.1747	.2703	-.634E-11
PAY_2 * COHORT_4	-.01449	.2700	-.130E-12
PAY_3 * COHORT_2	.2837	.2020	-.536E-11
PAY_3 * COHORT_3	.5156	.2327	-.749E-11
PAY_3 * COHORT_4	-.08961	.2527	-.302E-13
WORK_2 * LNMAGE	-1.204	.4693	.336E-10
GENDER_2 * LNMAGE	-.09694	.5728	.723E-11
Deviance	= 2272.91	df =	8303

Figure 5.5 Parameter Estimates for Regression model after dropping ln(age) - Gender Interaction

Name	Parameter Estimate	Std.Err.	Score
%CON	5.826	.1071	-.151E-06
LNMAGE	5.680	.2681	-.957E-07
RACE_2	-.1685	.1570	-.392E-07
GENDER_2	-.4102	.1536	-.215E-06
PAY_2	.09588	.1510	-.134E-07
PAY_3	-.5523	.1387	-.424E-07
COHORT_2	-.07683	.1412	-.517E-07
COHORT_3	-.3076	.1542	-.143E-06
COHORT_4	-.1703	.1774	-.102E-07
WORK_2	-.1562	.1028	-.121E-07
INTERNAL_2	-.08259	.08198	-.175E-07
INTERNAL_3	.04013	.3374	-.806E-08
FACIL_2	-.1192	.08564	-.172E-07
RACE_2 * GENDER_2	.9054	.3120	-.778E-07
COHORT_2 * GENDER_2	-.5883	.2876	-.105E-06
COHORT_3 * GENDER_2	-.5386	.3759	-.348E-06
COHORT_4 * GENDER_2	.2166	.2554	-.137E-07
PAY_2 * COHORT_2	-.01015	.2234	-.546E-08
PAY_2 * COHORT_3	.1742	.2703	-.147E-07
PAY_2 * COHORT_4	-.01506	.2700	-.108E-08
PAY_3 * COHORT_2	.2837	.2020	-.708E-08
PAY_3 * COHORT_3	.5155	.2327	-.608E-07
PAY_3 * COHORT_4	-.09001	.2527	-.113E-08
WORK_2 * LNMAGE	-1.205	.4696	.357E-08
Deviance	= 2272.93		df = 8304

Figure 5.6 Summary of Stepwise Elimination of interaction terms from regression model

ln(rate)=ln(age)+race+gender+pay+cohort+work+internal+facility+race*gender
+cohort*gender+work*ln(age)+pay*cohort+gender*ln(age)
Deviance=2272.91, d.f.=8303

ln(rate)=ln(age)+race+gender+pay+cohort+work+internal+facility+race*gender
+cohort*gender+work*ln(age)+pay*cohort
Deviance=2272.93, d.f.=8304
Change in deviance on dropping gender-ln(age) interaction = 0.02, 1 d.f.

ln(rate)=ln(age)+race+gender+pay+cohort+work+internal+facility+race*gender
+cohort*gender+work*ln(age)
Deviance=2280.40, d.f.=8310
Change in deviance on dropping pay-cohort interaction = 7.5, 6 d.f.

With the results of the stepwise evaluation of interaction terms, we made the following decisions about the inclusion of interaction terms in our final baseline regression model.

1. *Age-Gender Interaction.* While we were concerned that age-specific mortality rates may have not been proportional by gender, our analyses using stepwise elimination of terms suggest that for all cancer an interaction term is not needed. The parameter estimate for the interaction is small compared to the gender main effect (Figure 5.5), and the change in deviance upon dropping the term was only 0.02 (1 d.f.). We dropped this interaction from our final model.

2. *Age-Employment Status Interaction.* As might be expected from sociological processes of worker selection and previous analyses of this cohort, the difference in health status between employed and terminated workers differs with age.[110] These differences increase with older age; workers still employed (or employed within the last two years) at older ages have lower mortality rates than those who left the workforce. Given the results of our stratified analyses and the apparent strong effect

of this interaction in our regression model (Figure 5.5), we retained this interaction in our final model.

3. *Paycode-Birth cohort Interaction.* Detailed analyses have been conducted for a range of causes of death among ORNL workers as part of a combined Oak Ridge facilities study.[114] These analyses emphasized the importance of considering paycode differences in mortality, and the changes in this relationship between birth cohorts. It is hypothesized these patterns in paycode effects reflect changes in the relationship between socioeconomic position (and perhaps associated behaviors such as cigarette smoking) and different causes of death. In our analyses of all cancer mortality, the largest paycode effects are between monthly and non-monthly paid workers, and these differences emerge only in later birth cohorts. Among workers in the earlier birth cohorts, monthly-paid workers did not have substantially lower cancer mortality rates than non-monthly paid workers. However, for those born after 1915, differences in mortality by paycode emerge and become important descriptors of cancer mortality. In our regression model the interaction between paycode and birth cohort accounts for only a change in deviance of 7.5 (6 d.f.); however, given previous analyses which examined a wider range of causes of death (and our interest in developing a model which could be applied to a range of causes of death), the interaction terms between paycode and birth cohort was retained in our final model.

4. *Race-Gender Interaction.* Similar to observations from other occupational and demographic descriptions of mortality in the United States, we found that the effects of racial differences in mortality differed by gender.[144] In this cohort, the highest cancer mortality rates were observed among non-white females and white males; the lowest mortality rates were among white females. Given the results of our stratified analyses and the strong association of this interaction in our regression model (Figure 5.5), we retained this interaction in our final model.

5. *Birth Cohort-Gender Interaction.* Our stratified analyses suggested that the age-adjusted difference in mortality rates between genders have changed over historical periods. The largest differences in cancer mortality rates between men and women were in the earliest birth cohorts. It may be likely that the largest differences were between white men and women who were paid non-monthly, and were born in the earliest birth cohorts; however, these three-way interactions can't be described in this model. Given the results of our stratified analyses and the parameter estimates in our final model (Figure 5.5), this interaction will be retained in our final model.

Our final model for demographic effects was as follows:

rate = lnage + gender + race + facility + paycode+ internal + birth_cohort + work + (lnage*work) + (race*gender) + (birth_cohort*gender) + (paycode*birth_cohort)

Table 5.22 Estimates of effect for terms in Baseline Model for All Cancer Mortality[†]

Variable	[Group]	Estimate	Std. error
Intercept		5.826	.1071
Lnage	[ln(age)]	5.680	.2681
Gender_2	[White Female]	-.4102	.1536
Race_2	[Non-White Male]	-.1685	.1570
Pay_2	[Paid Hourly]	.09588	.1510
Pay_3	[Paid Monthly]	-.5523	.1387
Cohort_2	[Born 1905-15]	-.07683	.1412
Cohort_3	[Born <1905]	-.3076	.1542
Cohort_4	[Born 1925+]	-.1703	.1774
Work_2	[Actively Employed]	-.1562	.1028
Internal_2	[Monitored]	-.08259	.08198
Internal_3	[Not Elig]	.04013	.3374
Facil_2	[More Than 1 Facility]	-.1192	.08564
Race_2 * Gender_2	[N-W Female]	.9054	.3120
Cohort_2 * Pay_2	[Born 1905-15, Paid Hourly]	-.01015	.2234
Cohort_2 * Pay_3	[Born 1905-15, Paid Monthly]	.2837	.2020
Cohort_3 * Pay_2	[Born <1905, Paid Hourly]	.1742	.2703
Cohort_3 * Pay_3	[Born <1905, Paid Monthly]	.5155	.2327
Cohort_4 * Pay_2	[Born 1925+, Paid Hourly]	-.01506	.2700
Cohort_4 * Pay_3	[Born 1925+, Paid Monthly]	-.09001	.2527
Cohort_2 * Gender_2	[Born 1905-15, Female]	-.5883	.2876
Cohort_3 * Gender_2	[Born <1905, Female]	-.5386	.3759
Cohort_4 * Gender_2	[Born 1925+, Female]	.2166	.2554
Work_2 * Lnage	[Actively Employed-ln(age)]	-1.205	.4696

[†] For different dose distributions, cell specific mean ages will change slightly leading to slight changes in parameter estimates.

Chapter Six - Radiation-Cancer Associations in the Checkoway Cohort

Overview

In these preliminary analyses, we restricted our study to the *Checkoway cohort*. The materials and regression model development for the expanded cohort, described in Chapters 4 and 5 were not used in these analyses. Rather, for analyses of the Checkoway cohort, we used the regression model which was developed for analyses reported previously.[19]

In contrast to previous reports about radiation-cancer associations among the Checkoway cohort of workers, these analyses consider follow-up through 1990 and focus on differences in the effects of radiation doses received at different ages. Since age at exposure may be associated with other time-related factors, we evaluate the consistency of our estimates between periods of hire, across periods of follow-up, and for different ages at risk.

Materials and Methods

Study cohort

These analyses were restricted to the Checkoway cohort, which includes white males hired before 1973 who worked at least 30 days and who had no known employment at other DOE facilities prior to 1978 (n=8307). Using the National Death Index, vital status was ascertained through 1990; death certificates were obtained for 97.5 percent of those who died in the Checkoway cohort. All cancer mortality was the outcome of interest in these analyses. Any death for which the underlying or contributing cause of death was assigned codes 140-209 of the Eighth revision of the International Classification of Diseases was considered a cancer death.

Statistical Methods

The selection of study covariates for the Checkoway cohort has been described previously.[19, 78] Briefly, age at risk was classified in five year intervals from under 25 years to ninety years and over. In Poisson regression analyses, age at risk was centered at 52.5 years, in a log-log relationship with cancer mortality; this has been shown to be an efficient method for controlling for the association between cancer mortality and age at risk.[71] Indicator terms were included for the following: birth cohort, which categorized workers born before 1905, born between 1905 and 1915, or born after 1915; paycode, which was used to control for socioeconomic differences in cancer mortality, was based on the worker's pay schedule when hired, and indicated whether or not a worker was paid on a monthly schedule; employment status, which indicated whether a worker had been employed within the last two years or not, and was used to control for mortality differences between actively employed and terminated workers; and, internal monitoring, which was lagged the same number of years as external dose, and indicated whether a worker was employed during those years when monitoring was conducted, and if so, whether the worker had ever been

tested for internal exposure. Cumulative external radiation dose was categorized in eight groups as follows: 0, -20, -40, -60, -80, -100, -120 and >=120 mSv. Terms were also included to describe differences between birth cohorts in the effect of paycode, and changes with age in the association between cancer mortality and employment status. In contrast to previously published analyses of this cohort, when calculating regression estimates of the percent change in cancer mortality per unit dose, we assigned values to categories of cumulative dose by using the cell-specific-mean dose (as described in Chapter 3).

The regression model for analyses of the *Checkoway cohort* was:

ln(cancer rate)=ln(age)+cohort+paycode+internal+work+age*work+pay*cohort+dose

Person-time and Events for Followup through 1990

By the end of follow-up in 1990, 2110 deaths were identified, of which 561 were cancer deaths. The distribution of person-years of observation and cancer deaths was examined in stratified analyses by demographic and employment variables (Table 6.1).

Table 6.1 Distribution of person-years and cancer deaths by study factors among the Checkoway Cohort

	Person-Years	All Cancer Deaths
Age		
<25	8522	1
25-45	113970	29
45-65	107404	235
65-85	24102	285
85+	409	11
Pay Code		
Monthly	118920	204
Non-monthly	135486	357
Birth Cohort		
<1905	15670	115
1905-1914	35927	184
1915-	202809	262
Employment Status		
Employed within last 2 years	104832	112
Not Employed	149574	449
Internal Monitoring Status		
Not Monitored	177587	358
Monitored	64169	197
Not Eligible to be Monitored	12650	6

Results

The estimated association between external dose and all cancer mortality for follow-up through 1990 was 1.8% increase per 10 mSv. In contrast to reports for follow-up through 1984, associations did not increase under longer lag assumptions (Table 6.2).

Table 6.2 Estimated Association Between Lifetime Cumulative Dose (under 10 and 20 yr Lags) and All Cancer mortality in the Checkoway Cohort.

	10 yr. lag	20 yr. lag
Percent increase per 10 mSv (se)	1.8 (0.9)	1.8 (1.1)
change in deviance for dose term	3.8	2.4

Model: ln(rate)= ln(age)+cohort+work+pay+internal+pay*cohort+work*ln(age)+dose.

The difference in parameter estimates between our analyses and those reported previously for follow-up through 1990 (2.05% per 10 mSv) appears to be due to our use of cell-specific mean doses.[32] When we assign values to dose categories using median dose categories, as previously done, dose response estimates for a 10 year lagged association increase to 2.02% increase per 10 mSv.

Age at Exposure

We evaluated whether the effects of radiation doses differed depending on the age at which exposure occurred. Examining Figure 6.1, the mean annual external radiation dose received by workers in the Checkoway cohort declined with older ages at exposure. A workers' cumulative dose received after a critical age was the sum of the annual doses received each year after that age (Figure 6.1).

Figure 6.1 Mean Annual External Radiation Dose by Age at Exposure

Doses Received at Older Ages

We examined dose response associations for cumulative doses received after a range of critical ages (Table 6.3). A 5.9 percent increase in total cancer mortality per 10 mSv dose received after age 45 was observed (change in deviance=10.6, 1 d.f.). A smaller magnitude of association was observed when annual doses received after age 40 were examined, with a somewhat smaller change in deviance upon inclusion of the dose term. When older critical ages were examined, larger, less precise dose response relationships were estimated, which were associated with smaller changes in deviance upon inclusion of the dose term. These analyses suggested that doses received after age 45 have a strong association with subsequent cancer mortality.

Table 6.3 Estimated Percent Increase in All Cancer Mortality per 10 mSv dose Received after a Range of Critical Ages, under a 10 year Lag Assumption.

	Lifetime Cumulative Dose (Age >=15)	Cumulative Dose received at Age >=40	Cumulative Dose received at Age >=45	Cumulative Dose received at Age >=50	Cumulative Dose received at Age >=55
% Increase	1.8	4.3	5.9	6.2	9.9
standard error	0.9	1.3	1.6	2.4	3.5
Change in Deviance for Dose Term	3.8	9.6	10.6	5.6	5.9

Model: ln(rate)= age+cohort+work+pay+internal+pay*cohort+work*age+dose. 10 year lag.

Doses Received at Younger Ages

As one way to assess potential confounding by exposures received at earlier ages, we conducted separate analyses for two subgroups of workers: those whose exposures were entirely accrued before age 45 and those whose exposures were entirely accrued at ages 45 and above. It should be noted that both analyses include those workers who had no recorded dose. Among those exposed only before age 45 (6316 workers, and 329 cancer deaths), the association between 10-year lagged cumulative dose and cancer mortality was poor fitting and of similar magnitude to its standard error (Table 6.4).

We were primarily interested, however, in assessing whether the association between dose received after age 45 and all cancer mortality was due to confounding by exposures received at earlier ages. Among those exposed *only* after age 45 (2657 workers, and 188 cancer deaths), the estimated association between 10 year lagged cumulative dose and cancer mortality was of larger magnitude and associated with a change in deviance of 3.4 (Table 6.4).

Table 6.4 Estimated Percent Increase in All Cancer Mortality per 10 mSv dose among Those Who Received No Exposure at Ages 45 and above, and Those Who Received no Exposure before age 45, under a 10 year Lag Assumption.

	Received Doses only at ages < 45	Received Doses only at ages >=45
% Increase per10 mSv (se)	3.02 (3.08)	8.55 (4.20)
Change in deviance for dose term (1 d.f.)	0.8	3.4

Model: ln(rate)= age+cohort+work+pay+internal+pay*cohort+work*age+dose. 10 year lag.

Adjustment Using Partitioned Cumulative Doses

We next examined the entire *Checkoway cohort*, stratifying the years of follow-up according to the cumulative doses received before and after age 45 (Table 6.5). In this table, one can examine the relative risk of cancer mortality by level of dose received after age 45, among workers with different levels of dose received before age 45. Relative risks tend to increase with increasing cumulative dose received after age 45, while there is little evidence of such an increase with increasing doses received before age 45.

Table 6.5 Estimated Relative Rate (RR) and Number of Cancer Deaths (d) by Age-specific Cumulative Doses, Under a Ten year Lag Assumption

	>=45 0 mSv RR (d)	>=45 0 - 20 mSv RR (d)	>=45 20 -40 mSv RR (d)	>=45 40 - 60 mSv RR (d)	>=45 60-80 mSv RR (d)	>=45 80-100 mSv RR (d)	>=45 100-120 mSv RR (d)	>=45 >=120 mSv RR (d)
<45 0 mSv	1 (136)	1.04 (60)	0.60 (3)	0.96 (2)	1.22 (2)	 (0)	 (0)	5.41 (4)
<45 0-20 mSv	1.21 (201)	1.15 (60)	1.11 (6)	1.00 (3)	1.73 (3)	3.30 (2)	 (0)	3.86 (2)
<45 20- 40 mSv	1.02 (14)	1.37 (16)	1.08 (2)	 (0)	1.01 (1)	7.28 (1)	 (0)	3.33 (1)
<45 40-60 mSv	1.27 (6)	0.90 (3)	1.15 (1)	2.83 (1)	2.40 (1)	 (0)	 (0)	4.83 (3)
<45 60-80 mSv	1.36 (3)	1.46 (2)	 (0)	 (0)	 (0)	 (0)	 (0)	 (0)
<45 80-100mSv	0.77 (1)	1.72 (2)	 (0)	 (0)	 (0)	 (0)	 (0)	 (0)
<45 100- 120mSv	1.38 (1)	 (0)	4.24 (1)	 (0)	27.02 (1)	 (0)	117.24 (1)	 (0)
<45 >=120mSv	1.11 (4)	1.12 (3)	 (0)	2.82 (2)	1.86 (1)	 (0)	1.92 (1)	3.12 (4)

model: cohort+work+pay+internal+age+wrk*age +pay*cohort +doseyg+doseold +doseyg*doseold

We were interested in evaluating whether the association between cumulative dose received after age 45 and all cancer mortality differed at different levels of cumulative

dose received before age 45 (Table 6.5); modification of the effects of late exposures by earlier exposures might be postulated, for example, if doses act at different stages of a muti-stage process. To allow an easier examination of this table, we calculated the relative risk of age-specific doses collapsed into four categories (Table 6.6).

Table 6.6 Estimated Relative Rate (RR) and Number of Cancer Deaths (d) by Age-specific Cumulative Doses in Four Dose Groups, Under a Ten year Lag Assumption

	>=45 0 mSv RR (d)	>=45 0 - 60 mSv RR (d)	>=45 60 -120 mSv RR (d)	>=45 >=120 mSv RR (d)
<45 0 mSv	1 (136)	1.01 (221)	0.99 (5)	5.56 (4)
<45 0-60 mSv	1.21 (65)	1.18 (92)	1.90 (8)	4.32 (6)
<45 60-120 mSv	1.20 (5)	1.16 (5)	4.82 (2)	-- (0)
<45 >=120 mSv	1.13 (4)	1.15 (5)	1.36 (2)	3.2 (4)

model: cohort+work+pay+internal+age+wrk*age +pay*cohort +doseyg+doseold +doseyg*doseold

Using a regression model, we evaluated modification of the effects of late exposures by earlier exposures by comparing a model which included interaction terms between the categorical terms for dose received before and after age 45, to a model with only main effects for older and younger doses. Inclusion of the interaction terms resulted in a change in deviance of 33.6 (with 46 d.f.), suggesting little evidence of interaction between age-specific doses. We also considered a model in which doses were categorized into four groups (as in Table 6.6); inclusion of the interaction between age-specific dose terms resulted in a change in deviance of 5.5 (with 9 d.f.). We concluded there was little evidence of modification of the effects of doses received after age 45 by doses received before age 45.

Table 6.7. presents estimates of the main effects in these model. The table reports rate ratios by level of dose received before and after age 45, controlling for effects of dose

received in the earlier, or later, age period. Relative risks were larger for the highest categories of exposure received after age 45, while there was little evidence of association between relative risks of cancer mortality and level of dose received before age 45.

Table 6.7 Estimated cancer mortality rate ratios for age-specific radiation doses

		0 mSv	0-20 mSv	20-40 mSv	40-60 mSv	60-80 mSv	80-100 mSv	100-120 mSv	>=120 mSv
Cumulative Dose received at Age >= 45 yr	Rate Ratio	1.00	1.01	0.77	0.91	1.47	1.54	1.56	3.32
	(# deaths)	(366)	(146)	(13)	(8)	(9)	(3)	(2)	(14)
Cumulative Dose received at Age < 45 yr	Rate Ratio	1.00	1.20	1.14	1.22	0.96	1.00	1.99	1.04
	(# deaths)	(207)	(277)	(35)	(15)	(5)	(3)	(4)	(15)

Model: ln(rate)= age+cohort+work+pay+internal+pay*cohort+work*age+(dose<45)+(dose>=45). 10 yr lag.

The association between cancer mortality and dose received after age 45 was next evaluated using a continuous term for mean cumulative dose received after age 45. We assigned values to dose categories using cell-specific mean doses, as discussed in Chapter Three. Replacing the indicator terms for dose received after age 45 with a single term for cumulative dose received after age 45 resulted in a change in deviance of 0.2 (6 d.f.). Similarly, the association between cancer mortality and cumulative dose received before age 45 was examined using a continuous term (the associated change in deviance was 2.7, 6 d.f.).

Doses received at ages 45 and above were associated with a 5.9 (se=1.7) percent increase in all cancer mortality per 10 mSv, after adjusting for doses before age 45 (Table 6.8). The association between doses received before age 45 and cancer mortality was weak, and slightly negative. The change in deviance for inclusion of the term for doses received after age 45, in a model that included a term for dose received before age 45, was 9.8 (1 d.f.). Doses received before age 45 contributed little to the

prediction of cancer mortality in the model which included a term for dose received after age 45. Under a 20 year lag assumption, the magnitude of the association between cumulative dose received after age 45 increased, although the goodness of fit of the association decreased.

Table 6.8 Estimated Increase in All Cancer Mortality per 10 mSv Cumulative Dose Partitioned in Two Age Groups

	10 year Lag		20 year Lag	
	Cumulative Dose received Before Age 45	Cumulative Dose received After Age 45	Cumulative Dose received Before Age 45	Cumulative Dose received After Age 45
Percent Increase	-0.7	5.9	0.6	7.4
standard error	1.2	1.7	1.2	2.5
Change in Deviance	0.3	9.8	0.2	6.9

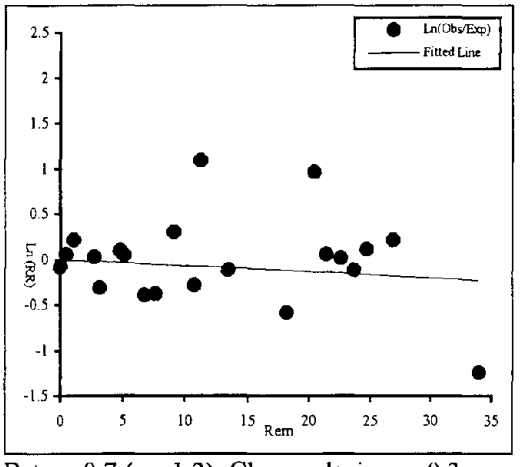
Model: age+gender+race+facility+pay-internal+cohort+work+age*work+race*gender+cohort*gender+pay*cohort+doseyg+doseold

To evaluate the improvement in fit due to partitioning cumulative dose by age at exposure, we compared the regression model which included separate terms for doses received at older and younger ages, Model 1: $\ln(\text{rate}) = ZB_z + B_1(\text{dose}<45) + B_2(\text{dose}>=45)$, to a model which included a single term for the sum of these age-specific cumulative doses, Model 2: $\ln(\text{rate}) = ZB + B_1(\text{dose}<45 + \text{dose}>=45)$, as described in Chapter 3. The difference in residual deviances between the two models (7.94, 1 d.f) represents the improvement of fit upon including an additional term to describe the separate of effects of doses received at two different age periods.

Examination of the ratio of observed to expected cancer deaths (figures 6.2, 6.4), support the conclusion that a dose response relationship exists primarily between doses received at older ages and cancer mortality, and that the association is much stronger than for lifetime cumulative dose (figure 6.3).

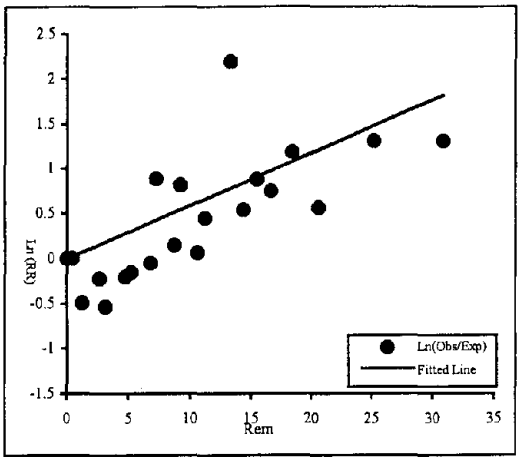
Figures 6.2 - 6.4 Ratio of observed to expected deaths and fitted line by dose

Figure 6.2 Cumulative dose received before age 45 adjusted for dose received at age >=45. 10 yr Lag



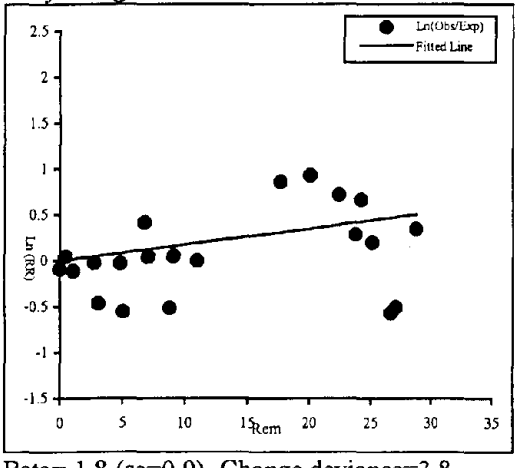
Beta= -0.7 (se=1.2) Change deviance=0.3
Model : ln(rate)=age+cohort+wk+pay+internal +pay*cohort+wk*age+doseyg+doseold.

Figure 6.4 Cumulative dose received at age >= 45 adjusted for dose received before age 45. 10 yr Lag.



Beta= 5.9 (se=1.7) Change deviance=9.8
Model : ln(rate)=age+cohort+wk+pay+internal +pay*cohort+wk*age+doseyg+doseold.

Figure 6.3 Lifetime Cumulative Dose, 10 yr Lag



Beta= 1.8 (se=0.9) Change deviance=3.8
Model : ln(rate) =age+cohort+wk+pay+internal +pay*cohort+wk*age+mndose

Applying Age-specific Weights to Annual Doses

We investigated weighting doses using other time-dependent functions as described in Chapter 3. The dose response associations for neither the linear (weighting function 3) nor the quadratic (weighting function 4) function fit the observed data as well as the dose response association under a step weighting function for a critical age of 45 years (Table 6.9). However, a dose response association in which annual doses are weighted under weighting function 5, did fit the data better, when exponents greater than thirty were considered; this weighting function approaches the step function but applies non-zero weights to younger ages at exposure. The estimated dose response relationship was 6.3 percent per 10 mSv (change in deviance=12.39, 1 d.f.) for doses weighted under function 5 (k=50).

Table 6.9 Estimated percent increase in cancer mortality per 10 mSv dose weighted by age at exposure among ORNL workers under a 10 year lag assumption.

	Weighting Function 3 age/45	Weighting Function 4 age^2/2025	Weighting Function 5 exponent k=10	Weighting Function 5 exponent k=30	Weighting Function 5 exponent k=50	Weighting Function 5 exponent k=100
% increase standard error	2.28 0.97	2.51 1.07	5.65 1.72	6.01 1.64	6.29 1.59	6.49 1.60
Change in Deviance with Dose Term	4.95	4.92	8.79	10.79	12.39	13.09

Model: ln(rate)= age+cohort+work+pay+internal+pay*cohort+work*age+dose. 10 year lag.

Additive Relative Risk Models

We examined the effect of using an additive relative risk model. The dose response association with lifetime cumulative dose under a ten year lag appeared to fit the multiplicative relative risk (Table 6.2) and additive (Table 6.10) relative risk models equally well. The residual deviance under the multiplicative relative risk model was 546.72; the residual deviance under the additive relative risk model was 546.59 (both models having 11 d.f.).

When doses received at age 45 and above were considered, the multiplicative relative risk model (Table 6.8) appeared to fit the data somewhat better than the additive relative risk model (Table 6.10). The residual deviance under the multiplicative relative risk model was 778.28; the residual deviance under the additive relative risk model was 779.78 (both models having 12 d.f.).

Table 6.10 Additive Relative Risk Model, 10 year Lag

	Lifetime Cumulative Dose	Dose received before age 45	Dose received after age 45
% Increase standard error	2.32 1.40	-0.63 1.33	7.68 3.74
Change in Deviance with Dose Term	3.9	0.2	8.2

In order to compare the magnitude of dose response estimates derived using multiplicative relative risk and additive relative risk models, we calculated estimates of the risk at 25 and 100 mSv received after age 45. 25 mSv dose received after age 45 was associated with a 1.19 fold increase in cancer risk under the additive relative risk model and with a 1.17 fold increase under a multiplicative relative risk model. 100 mSv dose was associated with a 1.77 fold increase in cancer risk under the additive relative risk model and with a 1.87 fold increase under a multiplicative relative risk model.

Examination of alternative hypotheses

These analyses demonstrated associations of substantial magnitude and very good fit between doses received at older age and cancer mortality. We next investigated hypotheses about potential time-related patterns of bias, confounding, or modification, that might account for these observed effects. The following hypotheses were considered:

1. These results reflect differences in radiation cancer associations between workers hired in early and later historical periods. Such differences might be hypothesized as a consequence of confounding due to the poorer health of workers hired during the World War II period, when radiation doses were received at older ages and at higher dose rates, or as a consequence of changes over time in the measurement of exposure.

2. These results reflect differences in the minimal latency periods associated with doses received at different ages.

3. These results reflect increases in the magnitude of dose response associations for deaths occurring at older ages, rather than increases in the magnitude of dose response associations for doses received at older ages.

4. These results reflect the decline in the association between cancer mortality and radiation with time since exposure; since cancer mortality occurs primarily at older ages, younger ages at exposure may be associated with longer time since exposure.

Each of these hypotheses is discussed in more detail, and empirically investigated.

Hire cohort

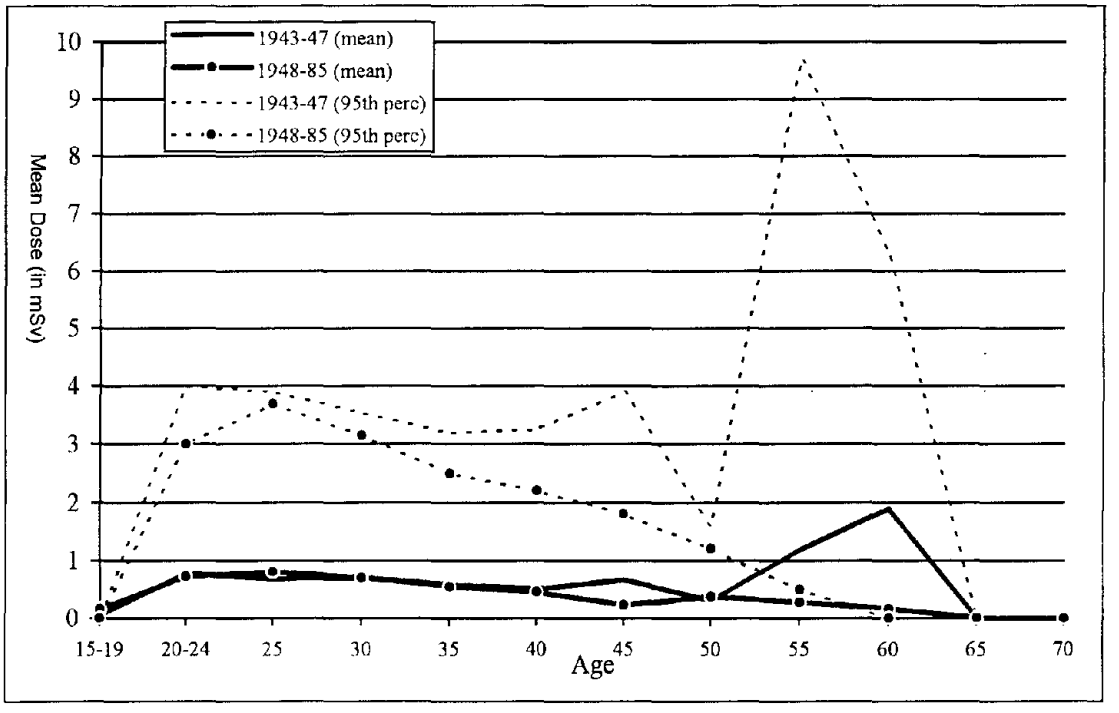
One explanatory hypothesis relates to potential confounding due to poorer health associated with earlier periods of hire.[82] Workers hired before World War II (WWII) were hired at older ages, and potentially suffered poorer health than workers hired after WWII, due to the military's selection of younger, healthier men out of the workforce (it should be noted that the assumption of the hypothesis that workers hired during the WWII period suffered poorer health than workers hired after the WWII period may not be valid[145]). Workers hired during the WWII period also tended to receive higher radiation doses, at higher dose rates, and at older ages, than workers hired in later years (Figure 6.5). Consequently, the observed association between doses received at older ages and cancer mortality could be due to the fact that doses received at older ages tended to be received in early years of operation among workers with poorer health.

Another reason to consider historical periods of employment relates to changes in exposure monitoring practices over time. Workers hired in the early years of operation at ORNL were monitored using different exposure assessment methods than workers hired later, which resulted in larger potential dose underascertainment.[79, 94, 97] This suggests that we might consider employment in the early years of operation not only as a potential confounder of dose response associations,[82] but also as a potential indicator of changes in exposure misclassification, leading to changes in estimates of dose response associations.

In order to evaluate whether dose response relationships differed between workers hired at different periods, in one set of analyses dose response associations were examined separately for workers hired between 1943-47 and workers hired after that period (the period 1943-47 has previously been used to define the WWII hire cohort in analyses of ORNL workers).[79] We examined whether the association between

cumulative dose and total cancer mortality differed between the cohort of workers hired between 1943 and 1947 (n=2193), and the cohort hired after 1947 (n=6114).

Figure 6.5 Pattern of Age-specific Exposure by Calendar Period



Among workers hired between 1943 and 1947, the association between *lifetime* cumulative dose and cancer mortality at ORNL was 3.4 (se=1.1) percent per 10 mSv, while among workers hired after 1947 this association was 0.3 (se=0.4) percent per 10 mSv. To estimate the change in deviance upon including an interaction term between period of hire and cumulative dose, we fit a model including interactions between all study covariates and an indicator for period of hire; upon inclusion of an interaction between dose and this indicator term the change in deviance was 3.12 (Table 6.11). However, exposures tended to be received at older ages among workers hired in the early years of ORNL's operation. We next examined the association between doses received after age 45 and cancer mortality for workers in each of the hire cohorts.

Table 6.11 Analyses of Modification of Dose Response Associations by Period of Hire

	Hired <1948 % incr (se)	Hired >=1948 % incr (se)	Change in deviance for interaction term between dose and Period of Hire
Lifetime Cumulative Dose	3.4 (se=1.1)	0.3 (se=0.4)	3.12
Dose Received After age 45	5.8 (se=2.2)	4.8 (se= 2.9)	0.11

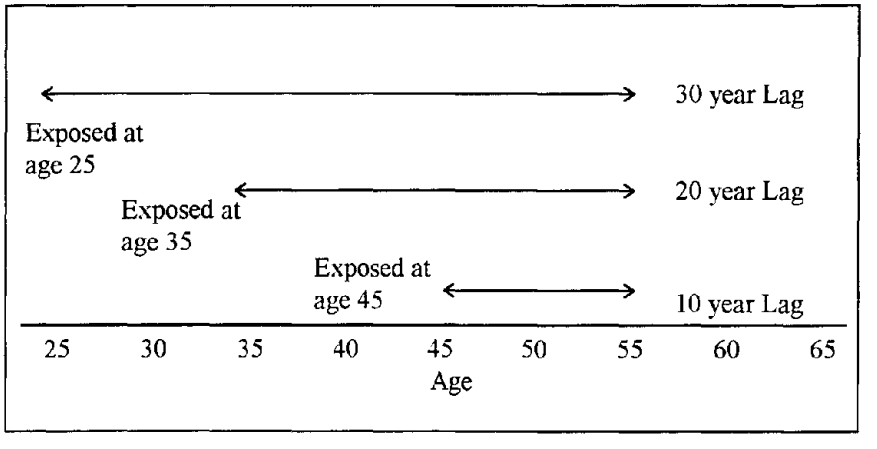
Considering doses received after age 45, the dose response association for the subcohort of workers hired after 1948 was similar in magnitude to the dose response association for the subcohort of workers hired before 1948. Among workers hired between 1943 and 1947 the association between cumulative dose received after age 45 and cancer mortality was 5.8 (se=2.2) percent per 10 mSv, adjusted for dose received before age 45. In the later hire cohort this association declined slightly to 4.8 (se= 2.9) percent per 10 mSv; the difference in these dose response associations between hire cohorts was small (change in deviance=0.11, 1 d.f.). These results suggest that differences in dose response associations between hire cohorts when considering lifetime cumulative dose may be explained as a consequence of differences in the ages at which exposures were received between hire cohorts.

Modification of Latency by Age at Exposure

Another hypothesized explanation for our findings is that radiation exposures may increase the incidence of cancer, but not the timing of when cancers appear. The possibility that doses received at younger ages are associated with longer latency periods has been suggested from studies of A-bomb survivors and patients receiving medical irradiation. It has been suggested that radiation-induced cancer may not appear among those exposed at earlier ages; rather cancer may occur in excess only at older ages when cancer typically develops in the unexposed. Under a relative risk model, in which cancer rates increase with age at risk, this suggests that exposures received at younger ages should be considered after longer latency periods than exposures received at older ages (Figure 6.6).

A related hypothesis suggests that high dose rates are associated with shorter latency periods than low dose rates. At ORNL exposures received at older ages primarily occurred in earlier calendar periods when dose rates were higher; longer latencies, then, might be considered for doses received more recently, which were received at earlier ages and at lower dose rates.

Figure 6.6 Latency Depends on Age at Exposure, Cancer Begins to Occur After Age 55



To investigate hypothesized differences in latency assumptions for doses received at different ages, we examined dose response associations for doses accumulated at younger ages with longer lag assumptions. We considered the fit and magnitude of dose response associations for exposures received before age 45, in a model which adjusted for any association between dose received after age 45 and cancer. While dose received before age 45 appears weakly, positively associated with cancer mortality under a 20 and 30 year latency assumption (Table 6.12), the magnitude and fit of these associations is far weaker than the magnitude and fit of associations between doses received at older ages and all cancer mortality. It does not appear that the differences in effect between doses received at older and younger ages are due to the necessity of considering longer lag assumptions for doses received at earlier ages.

Table 6.12 Estimated Association between Dose received Before age 45 and all cancer mortality under 10, 20, and 30 year lag assumptions

	Exposures received <45 10 year Lag	Exposures received <45 20 year Lag	Exposures received <45 30 year Lag
% Increase (se)	-0.67 (1.18)	0.59 (1.25)	0.40 (2.37)

Model: ln(rate)=ln(age)+cohort+work+pay+internal+pay*cohort+work*ln(age)+doseyg+doseold

Age at risk

Gilbert et al. have reported that, among workers at ORNL and Hanford, cancer deaths occurring at older ages were more strongly associated with radiation exposure than cancer deaths occurring at younger ages. They suggested that this may reflect a pattern of confounding, in which smoking-related cancer mortality was related only to deaths occurring at older ages and among workers receiving higher radiation doses.[71, 75]

Since doses received at older ages can only be associated with deaths at older ages, this suggests an alternate explanation for the observed increased radiation-cancer association with older age at exposure. We considered whether the modification of radiation effects by age at exposure could be explained as a consequence of increasing radiation effects with older ages at risk. We evaluated dose response associations separately for deaths occurring at older (>=70 years) and younger ages (<70 years).

Lifetime cumulative dose was evaluated first. For deaths occurring at ages less than 70 years there was an estimated 0.3 (se=1.1) percent increase in cancer mortality per 10 mSv lifetime cumulative dose; for deaths occurring at ages greater than 70 years the estimated association was 5.5 (se=0.7) percent increase per 10 mSv. To estimate the change in deviance upon including an interaction term between periods of age at risk and cumulative dose, we fit a model including interactions between all study covariates and an indicator for age at risk greater than 70 years; upon inclusion of an interaction between dose and this indicator the change in deviance was 7.20 (Table 6.13). This is consistent with Gilbert et al.'s observation of increasing association of lifetime cumulative dose with deaths occurring at older ages.[71]

Table 6.13 Analyses of Modification of Dose Response Associations by Age at risk

	Age at Risk < 70 yr % incr (se)	Age at Risk >=70 yr % incr (se)	Change in deviance for interaction term between dose and age at risk
Lifetime Cumulative Dose	0.3 (se=1.1)	5.5 (se=1.5)	7.20
Dose Received After age 45	4.6 (se=2.8)	8.4 (se=2.4)	1.13

We next considered the effects of doses received after age 45. Doses received after age 45 were associated with cancer mortality at younger and older ages. For deaths occurring at ages less than 70 years, cumulative dose received after age 45 was associated with a 4.9 (se=2.8) percent increase per 10 mSv, while for deaths occurring at ages greater than 70 years cumulative dose received after age 45 was associated with an 8.6 (se=2.4) percent increase per 10 mSv.

Time Windows of Exposure

Time-windows of exposure were one of the time-related factors of interest at the outset of this study. However, our findings of the substantial impact of age at exposure on the magnitude and trends of dose response associations offered an alternative direction to focus analyses.

Time-windows, however, offered another hypothesized explanation for the observed modification of dose response relationships by age at exposure. Under a hypothetical 20 year time-window, which is bounded by a 10 year lag and disregard of exposure more than 30 years after exposure, cancer mortality at older ages is only associated with doses received at older ages. For example, a cancer death occurring at age 70 would be associated with doses accrued only between ages 40 and 60, and a cancer death occurring at age 80 would be associated with doses accrued only between ages 50 and 70. So, for older ages at risk, the effects of age at exposure and time windows of exposure would be difficult to distinguish.

In studies of long term, low level exposures, there is a limited range of time-window scenarios to consider. Some minimum lag assumption typically is made (for example 10 years), and a time-window must be broad enough to allow a range of doses to be accrued (the window must include 10 to 20 years of exposure accrual). We compared results from analyses using a twenty year time-window under a 10 year lag assumption to results in which cumulative dose was partitioned by age at exposure.

Using this time-window of exposure, the estimated association was 2.58% (se=1.01) increase per 10 mSv (change in deviance=5.7, 1 d.f.). The magnitude and goodness of fit of this dose-response association was smaller than when considering the effects of age at exposure (Table 6.8); this time-window of exposure did not appear to provide a strong alternative to age at exposure.

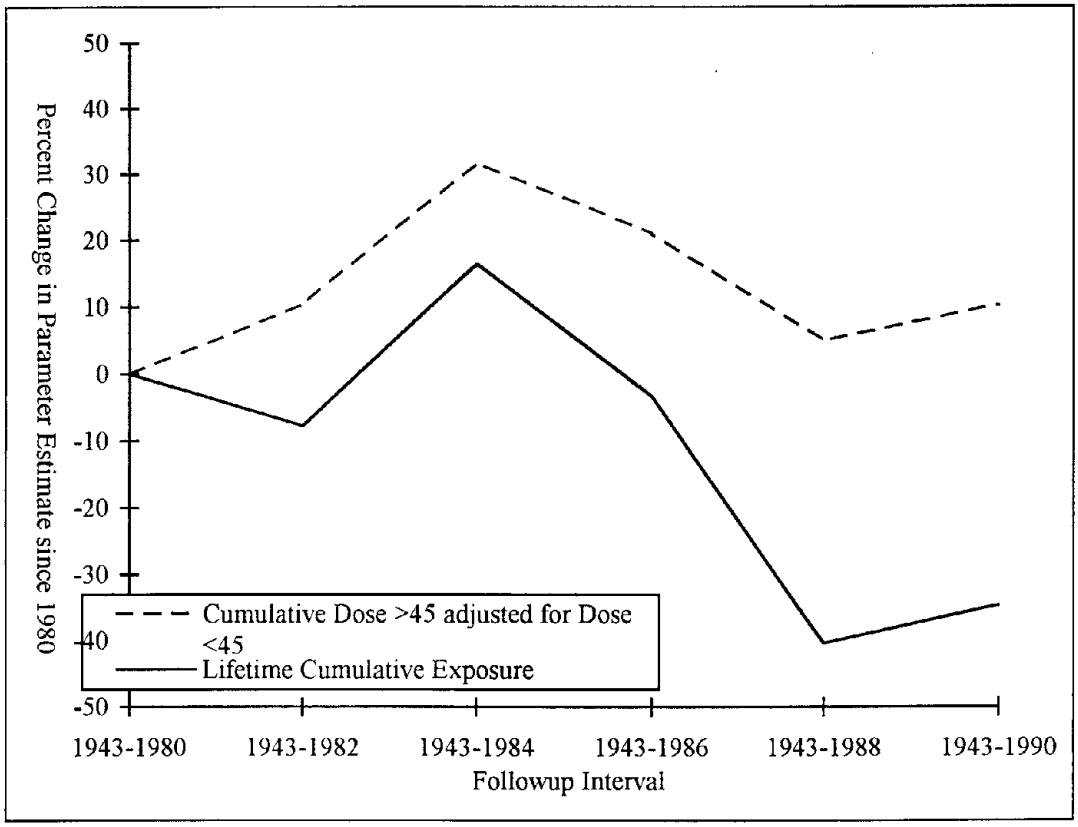
The distinction between time-windows of exposure and age at exposure would be most discernible at younger ages at risk. At younger ages at risk, time-windows of exposure relate cancer mortality to doses received at younger ages. We investigated whether exposures received in the previously defined time-window of exposure were predictive of mortality at younger ages at risk (less than 70 years); or, if time-windows of exposure were only predictive of cancer mortality at older ages at risk, when time window of exposure and age at exposure define the same periods of exposure. For ages at risk less than 70 years, doses received in this time-window were associated with a 0.62% (se=1.27) increase in all cancer mortality (change in deviance 0.2, 1 d.f.). Again, this suggests that this time window of exposure does not provide a strong alternative to age at exposure.

Period of Followup

The stability of the association between radiation dose and cancer mortality over periods of follow-up was of interest for two reasons. Firstly, our analyses of the effects of age at exposure were partially the consequence of previous observations that the magnitude of radiation-cancer dose response associations within the Checkoway cohort declined with increasing length of follow-up. With inclusion of the last ten years of vital status follow-up, the dose response association for all cancer mortality under a 10 year lag assumption declined 33 percent, from 2.7 (se=1.4) percent per 10 mSv for follow-up through 1980, to 1.8 (se=0.9) percent per 10 mSv for follow-up through 1990 (Figure 6.7). Secondly, there is evidence of declining completeness of vital status ascertainment for the last years of follow-up (Figure 4.1). In order to assess whether this change in ascertainment led to substantial bias in dose response associations, we evaluated these associations after excluding more recent years of follow-up data.

When exposures received after age 45 were considered, dose response estimates were relatively stable with increased follow-up, changing from 5.6 (se=1.4) percent per 10 mSv for follow-up through 1980, to 6.3 (se= 1.7) percent per 10 mSv for follow-up through 1990 (Figure 6.7). The magnitude of the dose-response relationship was robust to the length of follow-up when differences in the effects of radiation exposures at different ages were taken into consideration. This finding is consistent with one of the preliminary hypotheses for this study, which suggested that some of the decline over time in the association between lifetime cumulative dose and cancer mortality may be due to the changing distribution of age at exposure.

Figure 6.7 Change in estimated dose response relationship for follow-up ending 1980-1990 for lifetime cumulative dose, and dose received at age => 45 adjusted for dose received at age <45



Lifetime cumulative dose Model: ln(rate) = age+cohort+wk+pay+internal+pay*cohort+wk*age+dose
Age-specific dose Model:ln(rate)=age+cohort+wk+pay+internal+pay*cohort+wk*age+doseyg+doseold

Conclusion

These analyses suggest that among workers in the Checkoway cohort, the association between cumulative dose received at older ages and subsequent cancer mortality was of large magnitude and good fit. Furthermore, this association was consistent between periods of hire and follow-up, and for deaths occurring at different ages, suggesting that by considering age at exposure, a smaller, more relevant time period of exposure has been identified.

Chapter Seven - Radiation-Cancer Associations in the Expanded Cohort

Overview

This chapter presents analyses, within the expanded cohort, of associations between external radiation dose and all cancer mortality. This is the first time associations between radiation and cancer have been reported for the expanded cohort of 14,095 workers. Chapters 4 and 5 presented our development of a baseline regression model for this cohort.

In this chapter we consider the association between all cancer mortality and lifetime cumulative dose under 5, 10, and 20 year lag assumptions. These analyses allow comparison of results to previous evaluations of the association between lifetime cumulative dose and cancer mortality among workers at ORNL, and to analyses of these associations in other populations of nuclear facility workers. Next, we considered the effects of age at exposure, which was demonstrated to be an important consideration in the Checkoway cohort workers (Chapter 6). We present analyses of the association between doses received at older ages and cancer mortality under 5, 10, and 20 year lag assumptions, and evaluate the effect of controlling for dose received at younger ages.

Lifetime Cumulative Dose, and Cumulative Dose Received at Older Ages

We first examined the association between external dose and total cancer mortality under 5, 10, and 20 year lag assumptions (Table 7.1). Associations increased slightly in magnitude and goodness of fit under longer lag assumptions. When compared to results from our analyses of the Checkoway cohort (Table 6.2), estimates were of similar magnitude and goodness of fit.

Following our analyses of the Checkoway cohort, we investigated the effects of exposures received at later ages. Under 5, 10, and 20 year latency analyses, dose response associations for exposures received after age 45 demonstrated the best fit in a model predicting all cancer mortality (Table 7.1). The magnitude of association was larger for doses received after age 50 than for doses received after age 45, although the goodness of fit for this association was smaller. The magnitude of association also increased with increasing lag assumptions, although the goodness of fit was largest under a ten year lag.

Table 7.1 Estimated Increase in All Cancer Mortality per 10 mSv by Critical Age and Lag

	5 Year Lag	10 Year Lag	20 Year Lag
Lifetime Cumulative Dose Critical Age=15			
Percent Increase	1.26	1.35	1.87
standard error	0.74	0.79	1.00
Change in Deviance	2.7	2.8	3.2
Critical Age = 40 years			
Percent Increase	2.98	3.29	4.28
(standard error)	0.97	1.06	1.55
Change in Deviance	8.00	8.09	6.19
Critical Age = 45 years			
Percent Increase	4.32	5.31	7.92
(standard error)	1.29	1.40	2.17
Change in Deviance	9.28	11.28	10.14
Critical Age = 50 years			
Percent Increase	5.33	6.39	9.52
(standard error)	1.85	2.10	3.63
Change in Deviance	6.82	7.46	5.3

Model: age+gender+race+facility+pay+internal+cohort+work+age*work+race*gender+cohort*gender +pay*cohort+dose.

Adjustment Using Partitioned Cumulative Doses

We next examined the associations between all cancer mortality and dose received at older critical ages, controlling for doses received at younger ages.

As in the previous analyses (Table 7.1), the magnitude of association between all cancer mortality and cumulative doses received at older ages tended to increase as older critical ages were considered, and under longer lag assumptions (Table 7.2).

However, after adjusting for doses received at younger ages, the improvement in model fit was largest for doses received after age 40 than for doses received after age 45 or 50, under five and ten year lag assumptions.

Table 7.2 Estimated Increase in All Cancer Mortality per 10 mSv Cumulative Dose Partitioned in Two Age Groups

	5 year Lag		10 year Lag		20 year Lag	
	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age
Critical Age = 40 years						
Percent Increase	-1.91	**3.33**	-1.71	**3.49**	-0.61	**4.29**
standard error	1.27	**0.82**	1.29	**0.90**	1.36	**1.35**
Change in Deviance	2.5	**12.1**	1.9	**10.9**	0.2	**7.5**
Critical Age = 45 years						
Percent Increase	-0.86	**4.39**	-0.69	**4.98**	0.24	**7.31**
standard error	1.05	**1.36**	1.05	**1.48**	1.12	**2.24**
Change in Deviance	0.7	**8.7**	0.5	**9.4**	0.4	**8.4**
Critical Age = 50 years						
Percent Increase	0.37	**4.01**	0.54	**5.28**	1.63	**7.68**
standard error	0.85	**2.10**	0.85	**2.27**	1.00	**3.78**
Change in Deviance	0.2	**3.2**	0.4	**4.7**	2.5	**3.4**

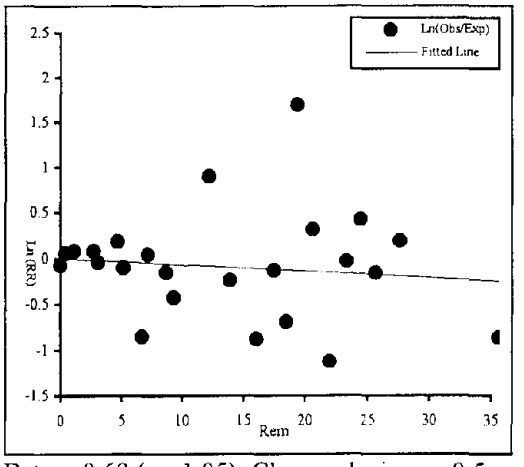
Model: age+gender+race+facility+pay+internal+cohort+work+age*work+race*gender+cohort*gender+pay*cohort+doseyg+doseold

Considering doses received before the critical age, coefficients are all negative for the youngest ages (less than 40 years), and smallest for the shortest lag assumption. Similar to analyses of the Checkoway cohort (Chapter 6), graphs of observed over

expected cancer deaths by dose were constructed to visually examine the fit of dose response models (figures 7.1, 7.2, 7.3).

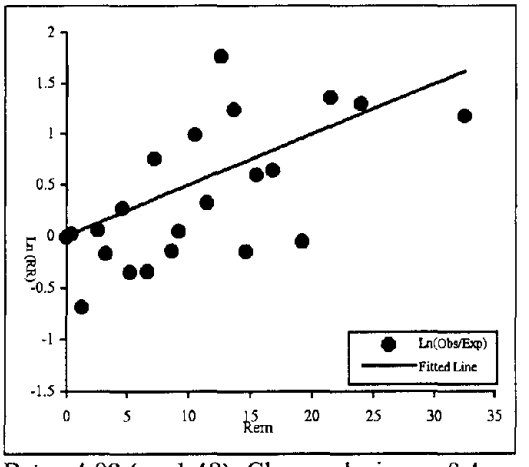
Associations for the expanded cohort tend to be of slightly smaller magnitude and poorer fit than associations observed among workers in the Checkoway cohort. For example, the association between cumulative dose received after age 45 and all cancer mortality under a ten year lag assumption in the expanded cohort (4.98% increase per 10 mSv; Table 7.2) is somewhat smaller than the association observed among workers in the Checkoway cohort (5.9% increase per 10 mSv; Table 6.8). This may, in part, reflect less complete follow-up for the expanded cohort, and poorer dosimetry data.

Figure 7.1 Cumulative dose received before age 45, adjusted for dose received at age >=45



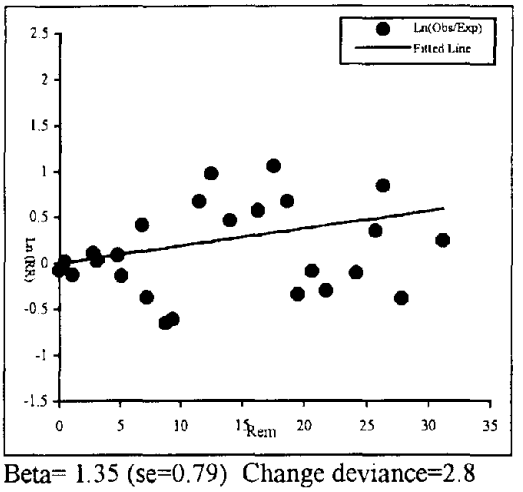
Beta= -0.69 (se=1.05) Change deviance=0.5
Model : ln(rate)=age+cohort+wk+pay+internal +pay*cohort+wk*age+doseyg+doseold.

Figure 7.3 Cumulative dose received at age >= 45, adjusted for dose received before age 45



Beta= 4.98 (se=1.48) Change deviance=9.4
Model : ln(rate)=age+cohort+wk+pay+internal +pay*cohort+wk*age+doseyg+doseold.

Figure 7.2 Lifetime Cumulative Dose



Beta= 1.35 (se=0.79) Change deviance=2.8
Model : ln(rate) =age+cohort+wk+pay+internal +pay*cohort+wk*age+mndose.

Additive Relative Risk Model

Considering an additive relative risk model for all cancer mortality under a ten year lag assumption, doses received after age 45 were associated with a 6.85 (se=3.10) percent increase in all cancer mortality per 10 mSv, adjusting for doses received before age 45 (Table 7.3). Inclusion of the term for dose received after age 45, in a model which already included a term for dose received before age 45, was associated with a change in deviance of 8.6 (1 d.f.).

The dose response association for lifetime cumulative dose under a ten year lag appeared to fit the multiplicative relative risk (Table 7.1) and additive relative risk (Table 7.3) models equally well. The residual deviance under the multiplicative relative risk model was 1874.1; the residual deviance under the additive relative risk model was 1873.9 (both models having 24 d.f.).

The dose response association for cumulative dose received after age 45 under a ten year lag appeared to fit the multiplicative relative risk (Table 7.2) only slightly better than the additive relative risk model (Table 7.3). The residual deviance under the multiplicative relative risk model was 2263.3; the residual deviance under the additive relative risk model was 2264.0 (both models having 25 d.f.).

Table 7.3 Additive Relative Risk Model, 10 year Lag

	Lifetime Cumulative Dose	Dose received before age 45	Dose received after age 45
Beta	1.72	-0.58	6.85
standard error	1.12	1.14	3.10
Change in Deviance with Dose Term	2.9	0.2	8.6

Women in the ORNL Cohort

There are 3,389 women in the expanded cohort who contribute 98,718 person-years of observation to these analyses (Table 4.3). One hundred twenty nine deaths due to cancer occurred among these women.

Women at ORNL tended to perform different types of jobs than men. Deaths among women at ORNL have primarily been among weekly-paid workers (Table 5.6), many of whom received little occupational exposure to radiation. A small number of analyses were conducted to evaluate the distribution of radiation exposures among women in this cohort, and to separately examine trends in the relative risk of cancer mortality among the women by level of cumulative external radiation dose. Given the limited distribution of deaths by exposure, separate tables person-time and events were constructed for women, in which dose was categorized in smaller dose categories (seven 10 mSv groups, ranging from 0 to 50+mSv). A regression model was used which included terms for age, race, paycode, birth cohort, employment status, internal monitoring, facilities of employment, and interactions between paycode and birth cohort, and between age and employment status.

The distribution of cancer deaths among women by level of radiation dose covers a small dose range. Only 16 cancer deaths occurred among women receiving greater than 10 mSv dose under a ten year lag, and only 1 death among women receiving greater than 50 mSv (Table 7.4). Examining the ratios of observed to expected cancer deaths by dose, relative risk of cancer among women increase with increasing lifetime cumulative dose under a 10 year lag assumption; however, these estimates were based on a small number of cancer deaths among the exposed women workers.

Table 7.4 Distribution of All Cancer Deaths Among Women by Lifetime Cumulative Dose, 10 year Lag

Dose Group	All Cancer Mortality **Observed**	All Cancer Mortality **Expected***	Observed /Expected
0	46	45.4	1.01
>10 mSv	67	72.1	0.93
>20 mSv	7	8.2	0.85
>30 mSv	5	1.5	3.33
>40 mSv	2	1.0	2.0
>50 mSv	1	0.2	5.0
50+ mSv	1	0.5	2.0

*ln(rate)=age+race+pay+cohort+work+internal+facil+pay*cohort+age*work

Analyses which examined dose-response associations for exposure received at older ages were further limited by the small number of events among exposed women workers (Table 7.5). Only three cancer deaths occurred among women who received more than 10 mSv dose after age 45.

Table 7.5 Distribution of All Cancer Deaths Among Women by Cumulative Dose Received After Age 45, 10 year Lag

Dose Group	All Cancer Mortality **Observed**	All Cancer Mortality **Expected***	Observed /Expected
0	115	112.2	1.02
>10 mSv	11	15.0	0.73
>20 mSv	1	1.6	0.63
>30 mSv	1	0.06	16.67
>40 mSv	0	0.04	--
>50 mSv	1	0.01	100.00
50+ mSv	0	0.07	--

*ln(rate)=age+race+pay+cohort+work+internal+facil+pay*cohort+age*work+doseyg

Conclusion

Workers at ORNL provide an important source of evidence about low level radiation effects, allowing consideration of 14,095 workers, each of whom had individual measurements of external radiation exposure and careful vital status follow-up. Cumulative dose received after age 45 strongly predicts all cancer mortality among these workers under a range of lag assumptions. Within the expanded cohort, associations between external radiation dose and all cancer mortality increased in magnitude as older critical ages of exposure were evaluated, and as longer lag assumptions were examined. The best fitting association was for cumulative doses received after age 45 under a ten year lag assumption. Adjustment for doses received at younger ages had little effect on these estimates. Evaluation of separate dose response associations for women in the expanded cohort was limited by the small number of cancer deaths which occurred among women who received radiation exposure. Results of these analyses for the expanded cohort were similar to our findings from analyses of the Checkoway cohort, although associations within the expanded cohort were slightly smaller in the magnitude and goodness of fit.

Chapter Eight - Associations Between Radiation and Other Causes Of Death

Overview

This chapter presents analyses, within the expanded cohort, of associations between external radiation dose and other selected causes of death. We considered associations with all cause mortality, all causes except cancer, lung cancer, all cancers except lung, leukemia, ischemic heart disease, non-malignant respiratory disease, and external causes.

Analyses of all cause mortality were conducted to examine the association between radiation and mortality using a category of death which was not dependent on death certificate retrieval or concerns about decisions in, or temporal trends in, cause of death coding. Among the ORNL workers, it has previously been observed that an excess of deaths are attributed to ill-defined causes, which, again, suggests limitations in the accuracy of classification of cause of death coding from death certificates.[19, 146]

While it has been suggested that radiation may be related to non-cancer causes of mortality, we conducted analyses of 'all cause mortality except cancer' with the expectation that evidence of strong associations between radiation and non-cancer mortality might suggest potential problems of confounding, or other analytical problems leading to biased dose response associations.

Analyses of lung cancer, and all cancer except for lung, were conducted in order to assess potential confounding due to smoking. If cigarette smoking were associated with radiation exposure, associations would be expected to be much stronger for lung

cancer than other cancers. Lung cancer deaths occurred in adequate numbers to permit separate analyses; and, by excluding lung cancers, we could assess the effect of lung cancer on the dose response association. Leukemia has been an outcome of interest in previous studies because of evidence of radiosensitivity.

Circulatory disease and non-malignant respiratory disease were examined to further assess hypotheses about confounding due to cigarette smoking. If smoking was positively associated with radiation dose, radiation would be expected to demonstrate a positive association with both of these causes of death. External causes of death were examined as an outcome presumed to have no association with external radiation.

Regression Models for analyses of Cause specific Mortality

A description of the distribution of deaths due to lung cancer, all cause mortality, ischemic heart disease, and non-malignant respiratory disease by study factors is presented in Appendix 2. Since our focus in these dissertation analyses was on all cancer mortality, our regression model was developed for all cancer mortality rather than for other causes of death. When examining non-cancer causes of death we used a Gompertz (log-linear) model for age at risk. Analyses of lung cancer and leukemia would not permit inclusion of either gender-cohort, or race-gender interactions because few of these cancer deaths were observed among women; for similar a reason, analyses of non-malignant respiratory disease do not include an interaction between race and gender (Appendix 2). Also, regression analyses of mortality due to non-malignant respiratory disease included only person-time accumulated after age 40, since no deaths due to non-malignant respiratory disease occurred before that age.

Lifetime Cumulative Dose

We examined the association between lifetime cumulative dose and cause specific cancer mortality under 5, 10, and 20 year latency assumptions (Table 8.1). All cause mortality under 5, 10, and 20 year lag assumptions exhibited a positive association with radiation dose. When cancer deaths were excluded from the category of all cause mortality, however, the goodness of fit of these associations was reduced. Associations between cumulative dose and lung cancer, and cumulative dose and all cancers except lung, were of comparable goodness of fit and magnitude under 10 and 20 year lag assumptions. All lymphatic and hematopoietic cancers, in contrast demonstrated little association with lifetime cumulative dose. The association between breast cancer and lifetime cumulative dose among women at ORNL could not be investigated since only two breast cancer deaths occurred among women whose lifetime cumulative dose (lagged five years) was greater than 0 mSv; these deaths occurred among women whose cumulative exposure was less than 20 mSv.

Ischemic heart disease (IHD) exhibited associations of small magnitude and poor fit; non-malignant respiratory disease exhibited a positive association with radiation dose under a ten year lag, however under 5 or 20 year lag assumptions the fit of this association was reduced. External causes exhibited almost no association with lifetime cumulative exposure.

Table 8.1 Dose response Estimates for Lifetime Cumulative Dose

Cause of Death	5 Year Lag % Increase se dev	10 Year Lag % Increase se dev	20 Year Lag % Increase se dev
All Cause	0.73 0.43 2.7	0.85 0.46 3.2	1.33 0.59 4.7
All Cause Except Cancer	0.43 0.54 0.6	0.58 0.57 1.0	1.04 0.74 1.9
All Cancers Except Lung Cancer	0.78 0.96 0.6	1.20 1.0 1.4	1.61 1.28 1.5
Lung Cancer	1.98 1.15 2.7	1.47 1.27 1.3	2.18 1.63 1.6
All Lymphatic and Hematopoietic Cancers	1.02 2.07 0.23	1.51 2.17 0.45	0.31 3.27 0.01
All Leukemia	1.80 2.98 0.33	1.88 3.08 0.34	2.36 3.94 0.32
Ischemic Heart Disease	0.60 0.80 0.5	0.34 0.88 0.1	1.42 1.12 1.5
Nonmalignant Diseases Of The Respiratory System	1.82 1.80 0.9	2.49 1.84 1.6	0.99 2.49 0.2
External Causes	-0.91 1.87 0.25	-0.20 2.02 0.01	2.69 2.59 0.96

Model: age+gender+race+facility+pay+internal+cohort+work+age*work+race*gender+cohort*gender +pay*cohort+dose.

Lung Cancer versus All Cancers except Lung

We examined associations between radiation doses received at older and younger ages, under 5, 10, and 20 year lag assumptions, with mortality due to all cancers except lung (Table 8.2) and with mortality due to lung cancer (Table 8.3). The goodness of fit and magnitude of associations were similar for all cancers except lung, and for lung cancer.

For all cancers other than lung, the magnitude of dose response associations for doses received at older ages, increased with longer lag assumptions, and when considering older critical ages. The best fitting association was observed for doses received after age 45 under a twenty year lag assumption. Doses received after age 45 were associated with estimates ranging from 3.88% (se=1.74) under a five year lag assumption, to 7.69% (se=2.64) increase in mortality per 10 mSv under a twenty year lag.

The magnitude of the association for lung cancer increased with increasing lag assumptions as well; for doses received after age 45 the association increased from 5.19% (se=2.21) under a five year lag assumption to 6.63% (se=4.18) increase per 10 mSv dose under a twenty year lag assumption (Table 8.3). As older critical ages of exposure were considered, the improvement in fit upon including the dose term declined; fewer workers accumulated doses at older ages (the distribution of deaths by lagged doses is shown in Table 8.5). Consequently there were few deaths due to lung cancer by levels of cumulative dose, when the critical age was set to 50 years.

Cumulative dose received after age 40 appeared to be the best predictor of lung cancer mortality. When considering doses received at the youngest ages (and under the shortest lag assumptions) an inverse association between dose and lung cancer was observed (Table 8.3). A similar pattern, though of poorer fit and smaller magnitude, was observed for cancer mortality other than lung (Table 8.2). This inverse association

between doses received at young ages, under short latency assumptions, and cancer mortality may, in part, reflect internal selection processes at ORNL.

Table 8.2 Estimated Increase in Cancers Other Than Lung Mortality per 10 mSv. Cumulative Dose Partitioned in Two Age Groups.

	5 year Lag		10 year Lag		20 year Lag	
	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age
Critical Age = 40 yrs						
Percent Increase	-0.73	**2.72**	-0.63	**3.17**	0.03	**4.21**
(standard error)	1.48	**1.11**	1.49	**1.17**	1.62	**1.67**
Change in Deviance	0.3	**4.7**	0.2	**5.6**	0.0	**4.8**
Critical Age = 45 yrs						
Percent Increase	-0.86	**3.88**	-0.75	**4.67**	0.36	**7.69**
(standard error)	1.33	**1.74**	1.34	**1.87**	1.38	**2.64**
Change in Deviance	0.4	**4.2**	0.3	**5.2**	0.1	**6.6**
Critical Age = 50 yrs						
Percent Increase	0.04	**4.12**	0.32	**5.44**	1.77	**8.32**
(standard error)	1.10	**2.57**	1.09	**2.76**	1.23	**4.35**
Change in Deviance	0.1	**2.3**	0.1	**3.3**	1.9	**2.9**

Model: age+gender+race+facility+pay+internal+cohort+work+age*work+race*gender+cohort*gender +pay*cohort+doseyg+doseold

Table 8.3 Estimated Increase in Lung Cancer Mortality per 10 mSv. Cumulative Dose Partitioned in Two Age Groups.

	5 year Lag		10 year Lag		20 year Lag	
	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age	Cumulative Dose received Before Critical age	Cumulative Dose received After Critical age
Critical Age = 40 yrs						
Percent Increase	-4.44	**4.19**	-4.12	**3.98**	-2.05	**4.41**
(standard error)	2.52	**1.18**	2.55	**1.41**	2.51	**2.33**
Change in Deviance	4.1	**8.0**	3.4	**5.4**	0.8	**2.6**
Critical Age = 45 yrs						
Percent Increase	-0.96	**5.19**	-0.75	**5.48**	-0.14	**6.63**
(standard error)	1.70	**2.21**	1.69	**2.45**	1.89	**4.18**
Change in Deviance	0.3	**4.5**	0.2	**4.1**	0.0	**2.0**
Critical Age = 50 yrs						
Percent Increase	0.82	**3.70**	0.74	**5.09**	1.25	**6.44**
(standard error)	1.34	**3.67**	1.35	**4.01**	1.70	**7.56**
Change in Deviance	0.4	**0.9**	0.3	**1.4**	0.5	**0.6**

Model: age+gender+race+facility+pay-internal+cohort+work+age*work+pay*cohort+doseyg+doseold

Leukemia Mortality

Analyses of leukemia were limited by the small number of events, distributed across a small range of doses. Consequently, analyses conducted examining shorter latency assumptions (5 and 10 yr lags), and categorized person-time and events in a smaller number of dose groups when evaluating doses partitioned by age at exposure (exposures were categorized in four dose groups as follows: 0, -20, -40, 40+ mSv). Regression models for leukemia, because of sparse events, do not include gender-cohort, or gender-race interactions. Analyses of leukemia consider the categories of all leukemia (ICD 204-207) and all lymphatic and hematopoietic cancers (ICD 200-209).

There was a limited distriubtion of events by cumulative dose received after age 45 with which to examine leukemias, or all lymphatic and hematopoietic cancers. Ther was a small number of events expected for any exposure categories above 40 mSv. Only one leukemia case was observed for exposure greater than 40 mSv. Because of the small number of events, estimates are extremely sensitive to a single event changing categories; and, estimated associations are evaluated across a very low range of dose.

Table 8.4 Observed and Expected counts for All lymphatic and haematopoietic cancers by doses received after age 45, under a 5 yr Lag assumption.

Dose gp	mean dose (in mSv)	pyrs (/100,000)	obs	exp	obs/exp
0 mSv	0	3.73385	67	66.2197	1.011784
-20	4.50978	.437250	28	29.448	0.950829
-40	28.3428	.039143	4	3.2661	1.224702
40+	88.5444	.044611	4	4.0657	0.98384

Table 8.5 Observed and Expected counts for All lymphatic and haematopoietic cancers by doses received after age 45, under a 10 yr Lag assumption.

Dose gp	mean dose	pyrs (/100,000)	obs	exp	obs/exp
0	0	3.87873	72	71.4048	1.008336
-20	.452384	.318808	23	25.3993	0.905537
-40	2.84193	.0274696	5	2.78484	1.795435
40+	8.53775	.0298472	3	3.41109	0.879484

Table 8.6 Observed and Expected counts for All leukemia by doses received after age 45, under a 5 yr Lag assumption.

Dose gp	mean dose (in mSv)	pyrs (/100,000)	obs	exp	obs/exp
0	0	3.73385	29	30.4919	0.951072
-20	4.50978	.437250	14	12.4366	1.12571
-40	28.3428	.0391429	3	1.58722	1.890097
40+	88.5444	.0446111	1	2.48431	0.402526

The category of all solid tumors (ICD 140-199) was compared to all lymphatic and hematopoietic cancers. All solid tumors demonstrate similar results to all cancers; leukemia, and all lymphatic and hematopoietic cancers demonstrate little association with cumulative dose received after age 45.

Table 8.7 Observed and Expected counts for All Solid Tumors by doses received after age 45, under a 5 yr Lag assumption.

Dose gp	mean dose (in mSv)	pyrs (/100,000)	obs	exp	obs/exp
0	0	3.73385	494	500.222	0.987562
-20	4.50978	.437250	209	218.631	0.955949
-40	28.3428	.0391429	28	25.1051	1.115311
40+	88.5444	.0446111	45	32.0420	1.404407

Table 8.8 Regression Model Results

	Doses Received Before age 45 Percent Increase/10 mSv (standard error)	Doses received after age 45 Percent Increase/10 mSv (standard error)
All lymphatic and hematopoietic cancers 5 year Lag	0.356 (3.285)	-1.304 (6.433)
All lymphatic and hematopoietic cancers 10 year lag	0.973 (3.297)	-1.937 (7.251)
All solid tumors 5 year Lag	-1.577 (1.316)	5.898 (1.775)

Followup through 1990. Doses in four groups. No race-gender or cohort-gender interactions.

Breast Cancer Mortality

Similar to analyses of leukemia mortaltiy, analyses of breast cancer mortality were limited by the small number of events, distributed across a small range of doses. Consequently, analyses conducted examining shorter latency assumptions (5 and 10 yr lags), and categorized person-time and events in a smaller number of dose groups (exposures were categorized in four dose groups as follows: 0, -20, -40, 40+ mSv).

Analyses were restricted to women in the cohort. Regression models for breast cancer, because of sparse events do not include gender-cohort, paycode-cohort, or gender-race interactions. Analyses consider the categories of female breast cancer (ICD 174).

No events were observed for exposure categories greater than 20 mSv; and, less than 0.05 cases were expected. Given the small distribution of events by exposure, dose-response analyses were not warranted.

Table 8.9 Observed and Expected counts for Female Breast Cancer by doses received after age 45, under a 5 yr Lag assumption.

Dose gp	mean dose	pyrs	obs	exp	obs/exp
0	0	.935228	22	21.6989	1.01
-20	.281116	.0511826	2	2.29790	0.87
-40	3.11895	.00052873	0	.00196261	0
40+	5.36344	.00024487	0	.00120068	0

Followup through 1990 for women only. Doses in four groups. No race-gender, paycod-cohort, or cohort-gender interactions.

Non-Cancer Mortality

We examined the association between radiation dose and non-cancer causes of death, considering all cause mortality, all cause except cancer, ischemic heart disease, and non-malignant respiratory disease. Deaths in these categories occurred in sufficient number to support dose response analyses (Table 8.4).

Table 8.10 Estimated Increase in Non-Cancer Mortality per 10 mSv.

	5 year Lag		10 year Lag		20 year Lag	
	Cumulative Dose received Before Age 45	Cumulative Dose received After Age 45	Cumulative Dose received Before Age 45	Cumulative Dose received After Age 45	Cumulative Dose received Before Age 45	Cumulative Dose received After Age 45
All Cause Mortality						
Percent Increase	0.29	**1.10**	0.42	**1.19**	0.38	**3.54**
(standard error)	0.59	**0.87**	0.58	**0.96**	(0.66)	**(1.42)**
Change in Deviance	0.3	**1.5**	0.5	**1.5**	0.3	**5.5**
All Cause except Cancer						
Percent Increase	0.61	**-0.30**	0.73	**-0.44**	0.34	**2.04**
(standard error)	0.69	**1.12**	0.70	**1.25**	(0.82)	**(1.81)**
Change in Deviance	0.8	**0.1**	1.0	**0.1**	0.2	**1.2**
Ischemic Heart Disease						
Percent Increase	1.62	**-2.39**	1.54	**-2.86**	1.09	**-0.16**
(standard error)	(1.01)	**(1.81)**	(1.03)	**(2.06)**	(1.22)	**(2.99)**
Change in Deviance	2.4	**1.9**	2.0	**2.1**	0.8	**0.0**
Non-malignant Respiratory Disease[†]						
Percent Increase	-1.77	**4.55**	-2.16	**5.66**	-2.42	**3.57**
(standard error)	3.23	**2.79**	3.32	**2.93**	(3.72)	**(4.95)**
Change in Deviance	0.3	**2.3**	0.5	**3.2**	0.5	**0.5**

[†] No race-gender interactions included in regression models.

The goodness of fit and magnitude of the association between dose received after age 45 and all cause mortality increased with longer lag assumption. Under a twenty year lag assumption, a 3.5 percent increase in all cause mortality was estimated per 10 mSv dose received after age 45 (change in deviance 5.5, 1 d.f.).

This association appeared to be due primarily to cancer causes of death. When all causes of death except cancer were considered, associations with radiation dose alternated from positive to negative with changing lag assumptions, and were of poor fit.

Associations between external dose received after age 45 and death due ischemic heart disease were negative under five, ten, and twenty year lag assumption. The fit of this negative association was largest under a ten year lag, while the change in deviance declined substantially under a twenty year lag assumption.

Non-malignant respiratory disease was positively associated with dose received after age 45. The magnitude and goodness of fit of this association was strongest under a ten year lag assumption (change in deviance 3.2, 1 d.f.), and declined under a twenty year lag assumption in part because no cases were observed at the highest level of exposure under a twenty year lag (Table 8.6).

Table 8.11 Observed and Ratio of Observed to Expected Deaths

Dose Received after Age 45 Cause of Death	0 rem Ratio (observed)	0 - 2 rem Ratio (observed)	2 - 4 rem Ratio (observed)	4 - 6 rem Ratio (observed)	6 - 8 rem Ratio (observed)	8 - 10 rem Ratio (observed)	10+ rem Ratio (observed)
All Cancer except Lung							
5 year Lag	0.98 (411)	1.00 (174)	0.98 (19)	1.25 (11)	0.80 (5)	0.79 (2)	1.94 (12)
10 year Lag	0.99 (436)	0.98 (155)	0.95 (16)	1.19 (9)	1.10 (6)	0.48 (1)	2.21 (11)
20 year Lag	1.00 (508)	0.94 (100)	1.30 (13)	0.72 (3)	0.39 (1)	3.85 (4)	2.86 (5)
Lung Cancer							
5 year Lag	0.98 (150)	0.91 (63)	1.43 (13)	1.30 (6)	0.94 (3)	2.14 (3)	1.89 (7)
10 year Lag	0.97 (157)	0.97 (62)	1.10 (9)	0.98 (4)	1.38 (4)	1.82 (2)	2.41 (7)
20 year Lag	1.00 (195)	0.85 (35)	1.52 (7)	1.0 (2)	2.73 (3)	2.5 (1)	2.86 (2)
All Cause							
5 year Lag	0.99 (2091)	1.01 (912)	1.13 (124)	1.07 (52)	0.90 (33)	0.85 (12)	1.30 (45)
10 year Lag	0.99 (2201)	1.01 (833)	1.15 (112)	1.03 (44)	0.92 (30)	1.02 (12)	1.59 (37)
20 year Lag	1.00 (2580)	0.96 (555)	1.10 (64)	1.19 (28)	1.15 (18)	1.78 (10)	1.51 (14)
Person-Years - 10 yr Lag	387,873	31,881	27,497	1,228	748	323	686

Table 8.12 Observed and Ratio of Observed to Expected Deaths for Non-Cancer Causes of Death

Dose Received after Age 45 Cause of Death	0 rem Ratio (observed)	0-2 rem Ratio (observed)	2-4 rem Ratio (observed)	4-6 rem Ratio (observed)	6-8 rem Ratio (observed)	8-10 rem Ratio (observed)	10+ rem Ratio (observed)
All Cause except Cancer							
5 year Lag	0.98 (1530)	1.03 (675)	1.13 (92)	1.00 (35)	0.93 (25)	0.70 (7)	1.06 (26)
10 year Lag	0.98 (1608)	1.03 (616)	1.22 (87)	1.01 (31)	0.84 (20)	1.06 (9)	0.95 (19)
20 year Lag	1.00 (1877)	0.99 (420)	1.03 (44)	1.36 (23)	1.22 (14)	1.25 (5)	1.08 (7)
Ischemic Heart Disease							
5 year Lag	1.01 (581)	1.03 (319)	0.94 (37)	0.96 (17)	0.54 (7)	0.64 (3)	0.90 (12)
10 year Lag	1.02 (624)	1.00 (286)	0.95 (33)	0.91 (14)	0.71 (8)	0.52 (2)	0.86 (9)
20 year Lag	1.02 (763)	0.91 (178)	0.94 (18)	0.80 (6)	1.06 (5)	1.21 (2)	1.29 (4)
Non-malignant Respiratory Disease							
5 year Lag	1.00 (93)	0.94 (53)	0.93 (7)	0.28 (1)	1.70 (5)	2.88 (3)	1.90 (5)
10 year Lag	1.00 (97)	0.90 (49)	1.00 (7)	0.61 (2)	1.49 (4)	4.42 (4)	1.78 (4)
20 year Lag	1.02 (110)	0.88 (42)	0.89 (5)	2.42 (6)	1.24 (2)	3.89 (2)	-- (0 / 0.9)
Person-Years - 20 yr Lag	411,179	12,492	975	399	214	93	134

Conclusion

Associations between external radiation doses received after age 45 and cancer mortality appear to be of similar magnitude for lung cancer and cancers other than lung, with better fitting associations for cancers other than lung when assuming latencies of ten year or longer.

All cause mortality was associated with radiation doses received after age 45, however this association was largely due to cancer deaths. Analyses of all cause mortality except cancer exhibited poor fitting associations with radiation. Ischemic heart disease exhibited negative, poor fitting associations with radiation doses received after age 45, while non-malignant respiratory disease showed positive associations with radiation.

Chapter Nine - Discussion

Interpretation of Major Findings

Workers at ORNL provide an important source of evidence about low level radiation effects, allowing analysis of 14,095 workers who had individual measurements of external radiation exposure and careful vital status follow-up. Cumulative dose received after age 45 strongly predicts all cancer mortality among these workers under a range of lag assumptions, and provides estimates of similar magnitude for lung cancer mortality and mortality from cancers other than lung. These analyses suggest that among workers at ORNL cumulative dose received at older ages was more strongly associated with subsequent cancer mortality than lifetime cumulative dose. The strong evidence of a dose response relationship, and the substantial magnitude of this association, suggest that by considering age at exposure we identified a smaller, more relevant time period of exposure.[147]

Theoretical models of carcinogenesis suggest reasons for increased sensitivity to radiation with increased age. Under multistage models of cancer development, the effects of an exposure may depend on the earlier initiation of a cell; with later age the probability of initiation increases, and consequently an exposure may be more strongly associated with cancer.[92] Increasing age is also thought to be accompanied by declining ability of the immune system and cellular repair mechanisms; this would provide another explanation for an increasing susceptibility to radiation-induced cancers with age.[16, 51] Analyses of chromosome aberrations (such as dicentrics, rings, and translocations) among radiation workers suggest that the occurrence of radiation-induced chromosomal aberrations increases with age.[46, 48]

Biases in these findings can occur through confounding and selection. There were a number of exposures which were not measured in this population. The effect of cigarette smoking, for example, could only be assessed indirectly with these data by examining tobacco-related causes of death. While general epidemiologic principles suggest that substantial confounding of dose response relationships by cigarette smoking is unlikely in an occupational cohort,[118, 119, 148] non-malignant respiratory disease did exhibit a positive association with dose received after age 45 in our analyses. While the fit of this association was not strong, it raises concern about potential confounding due to smoking.

Counter to the conclusion that smoking was a substantial confounder however, is the evidence of negative associations between dose received after age 45 and ischemic heart disease. Cigarette smoking would be expected to be associated with heart disease mortality as well as non-malignant respiratory disease. More importantly, however, any association between cancer and cigarette smoking would be expected to be much stronger (six- to ten-fold) for lung cancer than for other cancers.[149] Radiation doses received after age 45, however, were strongly associated with cancers other than lung; in fact, under a twenty year lag assumption, dose received after age 45 was a stronger predictor of mortality due to cancers other than lung than of mortality due to lung cancer. It has been noted that relative risks for lung cancer greater than 1.5 are unlikely to be due to confounding by cigarette smoking, while for cancers other than lung, uncontrolled confounding due to cigarette smoking is unlikely to explain even smaller associations.[92, 119]

Hypothesized patterns of confounding need to conform to the time-related patterns of these findings. In order for smoking to account for these results, for example, smoking patterns would have to be more strongly associated with radiation dose accumulated after age 45 than with lifetime cumulative dose; and, this pattern of confounding would have to persist between periods of hire (Chapter 6). Similarly, in

order for confounding by cigarette smoking to account for the increasing magnitude of association between doses received age 45 and all cancer mortality under longer lag assumptions, smoking would have to be more strongly associated with past exposures than total cumulative exposure. Counter to this conclusion, however, under a twenty year lag assumption radiation doses received after age 45 were more strongly associated with deaths due to cancers other than lung than with lung cancer (Tables 8.2, 8.3).

A possible explanation for the observed association between radiation and non-malignant respiratory disease relates to misclassification in cause of death coding. Previous studies, which have compared cause of death coding on death certificates to autopsy data, have reported that the detection rate for respiratory cancer deaths using death certificates was only 54%. When cancers were misclassified on the death certificate they were usually attributed to non-cancer diseases of the same organ system.[123] The category of non-malignant respiratory disease may include misclassified cancers of the respiratory system. Cancer indications, however, were of relatively high specificity; most deaths classified as due to cancer actually were due to cancer.

While occupational exposures other than radiation occurred at ORNL, in previous analyses neither consideration of job titles, which were used as an indicator of occupational exposures other than radiation, nor evaluation of potential exposure to beryllium, lead, and mercury, substantially changed estimates of the association between radiation and cancer mortality.[82] This dissertation does not examine the use of job titles to assess potential confounding by non-radiation occupational exposures of the association between cancer and age-specific radiation doses.

The consistency of our findings across periods of hire, ages at risk, and periods of follow-up supports our interpretation of these findings as evidence of modification of

the effects of radiation by age at exposure. The dose response association for workers hired after 1948 was similar in magnitude to the dose response association for workers hired before 1948 (Table 6.11). Such similarity argues against the conclusion that confounding related to hire in the early periods of operation at ORNL was present, and against the contention that biases in exposure measurement in the early years of exposure monitoring would account for observed dose response associations.

Differences in the effects of radiation were better explained by age at exposure than by age at risk; doses received after age 45 were more strongly associated with cancer mortality than lifetime cumulative dose for deaths occurring at younger and older ages. This argues against the suggestion that smoking, or another unspecified form of bias, was responsible for increased dose response associations for deaths at older ages.[71]

Finally, the magnitude of the dose-response relationship was robust to the length of follow-up when differences in the effects of radiation exposures at different ages were taken into consideration. The consistency of the dose response associations for exposures received after age 45 suggests that some of the decline over time in the association between lifetime cumulative dose and cancer mortality may be due to the changing distribution of age at exposure. Such consistency does not support the conclusion that lower levels of death certificate retrieval in the later years of follow-up of this cohort led to substantial bias in dose response estimates.

Since our analyses focused on cumulative doses received at older ages, we controlled for confounding by doses received at earlier ages. The fit and magnitude of these associations was changed very little, however, by controlling for dose received before age 45. Cumulative dose received before age 45 was only weakly associated with death due to cancer. The results of our investigation of more sophisticated weighting functions (Chapters 3 and 6) was initially surprising. We had expected that a smoothed weighting function would provide a substantial improvement in fit for dose

response associations compared to a step weighting function; however, the improvement in fit when using a smoothed weighting function was relatively small (Chapter 6). In retrospect this finding may not be surprising. The assumption for using a weighting function other than a step function had been that, biologically, it seemed improbable that radiosensitivity would change (from no radiosensitivity to a uniform level of radiosensitivity) at one age, either for a particular individual or for everyone in a population.[21] When considering a population, however, in which there is substantial variability in individuals' experiences of the biological process of aging and in the associated changes in radiosensitivity with age, a model for a critical age of exposure may be as adequate as a complicated weighting function designed to reflect hypothesized changes in radiosensitivity for an individual.

The magnitude of dose response associations for doses received after age 45 increased with longer lag assumptions. Gofman has suggested that associations between radiation and cancer mortality may increase with follow-up faster than the association of cancer mortality with age.[4] This would lead to larger estimated radiation effects with longer lag assumptions, and evidence of modification of dose response associations by time since exposure. Our analyses were limited to considering twenty year lag assumptions; our results suggest the need for further follow-up of this cohort to consider the effects of longer lag assumptions. Counter to the suggestion that doses received at younger ages may require longer latencies before the occurrence of cancer mortality, we did not observe evidence of substantial associations between doses received before age 45 and cancer mortality under 10, 20, or 30 year lag assumptions (Table 6.12).

Our analyses focused on all cancer mortality. Since all cancer mortality has been studied in previous analyses of DOE workers, including earlier analyses of this cohort, this allowed comparison of results between studies.[16, 19, 71] If the category of all cancers was overly broad--mixing radiosensitive with non-radiosensitive cancers--

results for specific radiosensitive cancers would be expected to stronger than results for all cancers. We did examine dose response associations separately for lung cancer and all cancers except lung, and observed associations of similar magnitude and goodness of fit for these outcomes (Tables 8.2 and 8.3).

The findings in this dissertation are particularly interesting because they are at odds with the orthodox position of epidemiologic literature on radiation health effects, which states that the effects of low level radiation are small and the associated relative risk declines with age at exposure.[27, 150] This review considers the literature on radiation-cancer associations among medically irradiated subjects and among A-bomb survivors in the LSS; and, this review discusses limitations of data from the LSS and medical irradiation studies for consideration of differences in the effects of radiation exposure with age.

Studies of Medical Irradiation

The literature on radiation exposures received in non-occupational settings has been cited as evidence that the effects of radiation exposure decline with age at exposure. In fact, however, this literature consists of contradictory findings, including several important studies of medical irradiation which support the conclusion that radiosensitivity may increase with older ages at exposure.

One important source of information about the health effects of medical irradiation comes from studies of ankylosing spondylitis (AS) patients treated with x-ray therapy. The primary effects observed after follow-up of over 14,000 ankylosing spondylitis (AS) patients treated with x-ray therapy was excess leukemia, primarily acute myeloid leukemia (AML).[151-153] Studies of these patients reported increasing relative risks of AML and leukemia with older age at exposure.[122, 153, 154] More recent studies continue to report overall increased relative risks for leukemia except chronic lymphocytic leukemia (RR=3.11), and AML (RR=3.12), with the largest relative risks

for exposures received after age 45.[155] More recent authors have attributed the increase in relative risk of leukemia with age at exposure to the effect of diminishing relative risk of leukemia with time since exposure. However, time since exposure and age at exposure were closely tied among these patients, and in analyses which adjust for time since exposure, the effects of age at exposure are diminished.

Another population which has been studied after receiving medical irradiation are women who experienced X-ray induced menopause (irradiation for metropathia haemorrhagica, MH). Findings of increasing radiosensitivity with age were reported by Smith and Doll, after follow-up of 2068 women.[156] They reported excess leukemia (RR=2.6) and cancers of heavily irradiated sites (RR=1.29) five or more years after treatment among patients who had an average of 13 years follow-up. The authors note, "The ratio of observed to expected deaths for cancers of the heavily irradiated sites increased with increasing age at first treatment, there being little excess in those treated under the age of 46 years." Darby et al reported on more recent follow-up of 2067 women treated for MH,[157] noting elevated SMRs for cancers of the heavily irradiated sites (SMR=1.46) and leukemia (SMR=2.05), and with older ages of first treatment relative risks for leukemia and cancer of the pelvic sites increased.

Inskip et al. also reported on leukemia among 4483 women irradiated for uterine bleeding.[158] Leukemia was in excess (SMR=2.0) as were all cancers (SMR=1.3). The authors note, "The SMR for leukemia increased from 0 for women who were 13 to 34 years old at the time of irradiation to 5.8 for women age 55 or older when treated." Regression analyses suggested that "the improvement due to adding a term for time since irradiation to the model that already included age at irradiation was marginal (p=.07)." The excess RR for women ages 35, 45, and 55 years at exposure were 1.6, 3.0, and 5.5% per cGy. A subsequent report by Inskip et al. confirmed these observations.[159]

In contrast, studies of tuberculosis (TB) patients exposed by fluoroscopy have not suggested differences in radiosensitivity with age. For example, Davis et al. reported on follow-up of 2074 women and 1277 men examined using fluoroscopy, noting that all cause mortality was high (women SMR=2.6; men SMR=1.9) due primarily to TB, and there was a deficit of lung cancer (SMR=0.8).[160] Breast and lung cancer were considered in relation to age at first exposure; however, few deaths due to cancer occurred among those exposed at older ages (only one breast cancer and six lung cancer deaths were observed among those first exposed after age 40). Patients were typically irradiated at younger ages, with the average age at first treatment being 28 years. Furthermore, exposure to fluoroscopy was extended over many years (up to five years), so age at first exposure was a poorer indicator of age at exposure than in studies of acute x-ray exposure. Finally, a deficit of lung cancer was not surprising since patients who underwent fluoroscopy had more advanced TB, often had parts of their lungs surgically removed, and may have been likely to quit smoking.[161]

Similarly, Davis et al. reported on follow-up of 6285 patients receiving fluoroscopy at an average age of first exposure of 33 years.[161] They reported no excess of cancer mortality (SMR=1.05), although non-cancer mortality was in excess, primarily due to deaths related to TB. Patients with lung surgery experience a 50% deficit of lung cancer. No excess of lung cancer was reported (SMR=0.8), but breast cancer mortality was slightly higher than expected(SMR=1.4) Consideration of differences in the effects of irradiation by age at first exposure for lung, breast, and esophagus cancer mortality compared those first exposed before, or after, age 30; no significant difference in effect was observed.

Studies of patients irradiated for tinea capitis (ringworm) and irradiation for treatment of enlarged thymus provide no information on the effects of exposures received at

older ages, since these analyses focus on the effects of irradiation of infants and children.[162-164]

Studies of the effects of exposure to diagnostic x-rays have given little attention to potential differences in effects of exposures at older age. Nearly all studies of diagnostic x-rays suffer from a lack of complete information on dental and medical exposures.[165-169]. A study by Inskip et al., for example, compared the history of medical diagnostic x-ray use among thyroid cancer patients and population based controls. While interest was directed at x-rays of the head and shoulder region (areas which might lead to irradiation of the thyroid gland) no information on dental x-rays was considered. Consequently, the mean number of x-rays among the cases and controls was extremely small (0.06 x-rays to head, neck, and spine among cases versus 0.04 among controls). A case-control study by Preston-Martin collected survey data on the history of diagnostic x-rays among 408 patients with salivary gland tumors and among neighborhood controls. Malignant tumors were strongly associated with radiation treatment to the head, which was primarily for acne (RR=4.6); risk for benign tumors increased with doses from diagnostic x-rays, and was greater for exposure before age 20 to a full mouth dental x-ray. However, younger age at first exposure was associated with earlier calendar years of exposure when much larger doses were received; when calendar year was entered in a regression model, age at first exposure had little effect. There was no control for cumulative dose in a time-dependent manner.

The Life Span Study and Age at Exposure

Survivors of the atomic bombings of Hiroshima and Nagasaki have been studied to evaluate the consequences of acute exposure to potentially large doses of external gamma radiation.[170] The conclusion from analyses of the Life Span Study (LSS) has been that the relative risk of radiation induced solid tumors, and many subtypes of

cancer, declines with older age at exposure.[150, 170] Estimates of relative risk for cancer presented in BEIR V were dependent upon age at exposure for cancers other than lung, and were dependent upon time since exposure for leukemia, lung and breast cancer.

For leukemia a distinction is made between those exposed before and after age 20.[3] The effects of radiation are described as being smaller for those exposed after age 20, while within each age group these effects are uniform. Early reports note that among the A-bomb survivors "there was a suggestion of an increase in RR with increasing age at exposure between the ages 40 and 60 years, but the association was not well defined."[158] Darby examined the effects of age at exposure among the LSS in some detail, presenting figures which suggest that the relative risk may not be uniform among LSS exposed after age 20. Rather these figures suggest an increase in RR for exposures received at older adult ages, with the RR for those exposed after age 55 comparable to the RR for those exposed before age 15.[122] In a recent report on leukemia, lymphoma, and multiple myeloma mortality in the LSS,[171] the authors note, "the largest excess risks appeared to have occurred among survivors who were under 20 or over 40 years old ATB, while little, if any excess risk apparent for survivors who were 20 to 39 years old ATB." They further compare the association to studies of the medical irradiation, writing, "Among adults exposed to radiation a positive association between leukemia risk and age at irradiation has been reported among the patients with ankylosing spondylitis and among women treated for benign gynecological diseases. The results of our study are generally in line with other studies."

In the LSS of atomic bomb survivors, the effects of external radiation on breast cancer appears to differ for exposures before or after age 15; for those exposed before age 15 effects are uniform, while for those exposed after age 15 effects decline with older age at exposure. This appears to be a consistent trend in the LSS study, though it may be

noted that while the estimated relative risk declines for ages of exposure older than 19, there is an upward tail to this trend. For those exposed at ages >=50 the RR is greater than for those exposed age 40-49.[172] It has been noted that the association between age at irradiation and breast cancer may be further complicated by factors such as age at first childbirth, which also appears to modify the effects of radiation on breast cancer incidence.[27]

Lung cancer in the LSS demonstrates a consistently increasing RR with increasing age at exposure (Figure 5-14 of BEIR V).[3] The relative risk for those exposed at age 60 appears roughly three-fold greater than the relative risk for those exposed at age 45, which itself was roughly twice as large as the relative risk for those exposed at younger ages.

Limitations of Studies of Medical Irradiation and the LSS for Understanding Age at Exposure

In contrast to studies of workers receiving occupational exposure to radiation which focus on radiation-cancer dose response associations, studies of TB and AS patients have focused on comparisons of cancer mortality among the patients to cancer mortality in the general population. This type of comparison has important implications for considerations of bias.

In studies of medical irradiation, patients enter the study with different levels of disease. For example, in comparison to the general population, TB patients suffered a 100% excess mortality from non-cancer causes.[160, 161] Nearly fifty percent of the mortality among these patients was due to TB or other non-malignant respiratory disease.[161] Similarly, AS patients suffered a 51% excess of non-cancer mortality.[154]

To the extent that the severity of disease with which the patient enters the study is correlated with radiation dose, age at exposure, or other factors of interest, these factors may confound study results on radiation effects. For many diseases, diagnosis and treatment at later stages of disease and older age suggest more severe disease and a worse prognosis. For a disease such as TB or AS, disease-related mortality may be more likely when treatment begins at older age; under these conditions, non-cancer, competing causes of mortality may be associated with age at first treatment. Consequently, cancer mortality rates may be less comparable to the general population for patients who begin treatment at older ages, since these subjects contribute person-time to calculations of the expected number of cancer deaths, but are dying in excess from non-cancer causes. When the outcome of interest is a disease such as cancer, for which there may be a ten to fifteen year latency, these competing causes of death may be particularly important.

When comparing results from studies of the LSS to our findings, differences should be noted in the populations studied and the factors that influenced survivorship after the bombing. As Nobel Laureate Oe Kenzaburo described them, the survivors were a select group, "people who, despite all, didn't commit suicide."[173] Stewart and Kneale have noted evidence of a correlation between sensitivity to early and late effects of radiation among those who survived the bombing, suggesting that the effects of age at exposure may be obscured in the LSS.[9, 28-30, 174] Premature deaths of people who were sensitive to the acute effects of radiation may have led to the selection out of people who were more sensitive to the later effects of radiation as well; consequently, when follow-up began five years after the bombing only a select population of less radiosensitive persons may have been left.[9, 14, 28]

The problems of estimating the exposures received by over one hundred thousand survivors of the atomic bombings using questionnaire data has occupied researchers for more than forty years.[175] Exposures received by people from the bombs were

affected not only by where the person was situated geographically, but also their body position at the time of the explosion, whether they were shielded from the explosion, the type of shielding material, atmospheric humidity, activities immediately after the explosion, and later ingestion of radioactive material.

Dose estimates for the BEIR III report in 1980 were based on exposure histories for 109,000 people collected by the ABCC and dose reconstruction efforts at ORNL; these were called the T-65 dose estimates. In the BEIR V report dose estimates were revised (under a new dosimetry system called DS86), and doses (specifically neutron doses at Hiroshima) were estimated to be lower than previously reported; each successive revision of the BEIR reports has lead to larger estimates of the associations between cancer mortality and low level radiation.[12] Because more information was required to calculate DS86 exposure estimates, there was insufficient data available with which to estimate exposures for many of the members of the LSS cohort, and so the study population was restricted to 75,991 survivors for analyses in the BEIR V report.

Another concern in comparing our findings to those from studies of medical or military sources of irradiation is that the pattern of exposure is significantly different. In contrast to studies of atomic bomb survivors, our study of ORNL workers is concerned with the effects of long term exposure to low level radiation, at low dose rates. Some have argued that radiation exposure received at low dose rates is less likely to lead cancer because cellular repair of mutations reduces the risk of cancer (referred to as a "dose rate effectiveness factor").[3] However, this conclusion comes largely from animal research, while there is little epidemiologic evidence supporting such effects;[4, 13, 150] in fact, in recent analyses of chromosomal aberrations, the contrary effect has been observed.[35] A study of stable chromosomal aberrations following radiotherapy for cervical cancer and benign gynecological disease found that lower dose radiation treatments resulted in higher aberration yields per unit dose.[40]

It might be noted that when considering high-LET radiation exposure among uranium miners, for the same total cumulative dose the relative risk for cancer appeared to be higher for longer duration, lower dose rate exposures. [176]

Directions for Further Research

These analyses have examined radiation-cancer associations among all demographic groups of workers at ORNL combined. We have not, however, considered potential differences in the effects of radiation between genders or between other sociodemographic groups. In this cohort there is little data for examining differences in dose response associations between men and women primarily because women received very low doses of radiation. Pooled analyses of women employed at several DOE facilities, which are currently undertaken, may be able to better address these questions.

These analyses also have not investigated differences in patterns of radiosensitivity with age for cancers types other than lung cancer. Potential differences in the magnitude of dose response associations for different types of cancers (such as, leukemia) and differences in patterns by age in radiosensitivity suggest an important question for future research.

Attention might also be directed at further investigating time-windows of exposure. Our analyses examined time-windows as an alternative to age at exposure analyses; however, to the extent that time-windows offer a possibility of refining identification of an etiologically relevant period of exposure, time-windows might be used in conjunction with age at exposure analyses. George Kneale has suggested methods for simultaneously estimating multiple time-related parameters, including lag and age at exposure; such methods might be applied for these analyses.

While data on external radiation exposures at ORNL are of relatively high quality and completeness, there are certainly reasons to expect exposure misclassification. As noted in Chapter Two, exposure misclassification may have been largest in the early years of ORNL's operation. While we attempted to evaluate this problem by considering dose response associations separately for earlier and later hire cohorts, with additional follow-up future research might evaluate in more detail the impact of changes in dosimetry methods on dose response associations.

Those workers in this cohort with the longest follow-up have been under surveillance for nearly fifty years; however, the average length of follow-up was thirty years and only 23% of the cohort has been followed to mortality. As follow-up is extended, and more mortality data are accumulated further examination of time-related factors, including lag and age at exposure, will be possible. Evaluation of changes in dose response associations under longer lag assumptions is of interest, particularly for estimates of the effects of doses received at younger ages.

Internal exposure to radionuclides is a source of exposure to ionizing radiation which is poorly measured in this cohort and which is a potential confounder of the association between external radiation and cancer mortality. Further analyses could investigate the use of job titles and periods of employment in order to evaluate potential exposure to internal deposition of radionuclides, as well as to evaluate potential confounding due to other occupational exposures.

Issues of selective employment, or healthy worker effects, suggest another source of confounding which might be empirically investigated in future analyses. Analyses might, for example, quantify the effect of using different criteria for minimum length of employment. In these analyses, workers employed less than 30 days were excluded; the impact on dose response estimates of using different criteria (such as a one year minimum employment) might be evaluated. Internal monitoring for radionuclides has

been suggested as an indicator of selective employment, in which workers with the best health status are screened into jobs with potential exposure to radionuclides. Another method for evaluating employment selection factors might be to examine differences in dose response associations among the subcohort of workers who were ever monitored, and among those never monitored for radionuclide deposition.

A substantial limitation of these analyses is the reliance on death certificate data. Information on the incidence of cancer would be of greater interest for these research questions than cancer mortality, which may be influenced, for example, by access to care, quality of treatment, and competing causes of death. Furthermore, comparisons of death certificate data to autopsy data suggest that 20 to 30% of neoplasms may be reported as non-neoplastic on the death certificate.[123, 177, 178] Analyses of the association between radiation and cancer incidence, however would require collection of new data or consideration of other study populations.

Conclusion

An estimated six hundred thousand workers have been employed by the DOE and its predecessor organizations in the nuclear industry,[12] and many more people have been affected by environmental releases of radiation from nuclear facilities and by medical and occupational radiation sources. Military uses for radioactive materials create further threats of radiation exposure. Despite the large number of people exposed to ionizing radiation, there has been little public participation in decisions about who should bear the risks created by nuclear technologies, or if we should bear them at all. Epidemiologic research on low level radiation needs to provide further information to the public about who is exposed, or at risk of exposure, and of the consequences of those exposure. To date, profits from nuclear technology have moved steadily to a handful of private contractors while the siting of waste facilities and the export of radiation abroad has often occurred among the poorest

communities.[179] Information about differences in sensitivity to radiation health effects needs to be coupled with more information about the sources of radiation exposure, in order to aid public evaluation of the dangers created by nuclear technologies.

These results raise important questions about the medical and industrial uses of nuclear technology. Similar to Stewart's findings of increased sensitivity of the fetus to radiation, these analyses contribute to evidence that older adults' sensitivity to radiation increases with age. The use of data from DOE cohorts is important for evaluating these questions. The results of cohort studies of badge-monitored workers, with extremely complete vital status follow-up deserve particular attention. We have identified age at exposure as an important determinant of differences in the effects of radiation among workers at ORNL. If, as these results suggest, the effects of low level radiation increase with age, then differences in radiosensitivity need to be incorporated into considerations of radiation protection, medical uses of radiation, and the implications of our industrial and military applications of this technology.

PLANNED PUBLICATIONS

Methods for creation of person-time data, which were developed for these analyses were published in the paper, Wood J, Richardson D, Wing S. "A Simple Program to Create Exact Person-Time Data in Cohort Analyses" International Journal of Epidemiology (1997), 26(2): 395-399.

Methods for investigating age at exposure, which were developed for these anlyses will be reported in the paper, Richardson D, Wing S. "Methods for Investigating Age Differences in the Effects of Prolonged Exposures." American Journal of Industrial Medicine (submitted).

Results of analyses of time-related factors among white male cohort of workers will be reported in the paper, Richardson D, Wing S. "Greater Sensitivity to Radiation Exposures at Older Ages among Workers at Oak Ridge National Laboratory: Follow-up through 1990." Lancet (submitted).

An additional publication reporting the results of anlayses of associations between radiation and cause specific mortality among the expanded cohort of workers will be submitted subsequently.

Appendix 1. Creating Observed over Expected Counts for Graphs

In order to create graphs of observed versus expected events, by level of cumulative dose, we summed observed and fitted events. The following tables describe the methods we used. If there were no observed deaths in a dose category i, then that we combined that dose category i with category (i-1). To combine two categories, we summed the observed and expected deaths for the two categories, and recalculate the population weighted mean dose for the combined categories.

If there were no observed deaths in two consecutive dose categories, i and (i+1), or any even number of consecutive dose categories, then we combined dose category i with dose category (i-1); and we combined dose category (i+1) with dose category (i+2). In this way, the person-time for the consecutive categories was divided evenly between the preceding and subsequent categories in which there were observed deaths. However, if there were no observed deaths in an odd number of consecutive categories, we included the extra person-time and expected events with the lower category in which an observed event occurred. Table 1. present sample data in which observed and expected counts are tabulated in one rem intervals; Table 2. shows how this data is collapsed when no deaths are observed in a dose category.

Appendix Table 1. Data in 1 rem categories

Dose Catg.	obs	exp	obs /exp	ln(obs /exp)	mean dose	pyrs/ 100,000	fitted value	exp(fitted)
0	593	598.895	0.990157	-0.009892	0	3.87873	0	1
>0	206	201.233	1.023689	0.023413	0.408135	0.302217	0.020333	1.020541415
>=1	11	21.8892	0.502531	-0.688098	1.25842	0.016591	0.062694	1.064701507
>=2	18	16.9213	1.063748	0.061799	2.64477	0.018896	0.131762	1.140837271
>=3	7	8.31737	0.841612	-0.172436	3.27643	0.008574	0.163232	1.177309491
>=4	10	7.64965	1.307249	0.267925	4.64366	0.007902	0.231347	1.260296664
>=5	3	4.24966	0.705939	-0.348227	5.23644	0.004378	0.260879	1.298071162
>=6	4	5.64465	0.708636	-0.344414	6.66942	0.004919	0.332271	1.394129916
>=7	6	2.82626	2.122947	0.752805	7.26453	0.002558	0.361919	1.436082449
>=8	2	2.31038	0.865658	-0.144265	8.66639	0.002262	0.43176	1.539964786
>=9	1	0.9576	1.044277	0.043325	9.25226	0.000963	0.460948	1.585575754
10	1	0.3712	2.693966	0.991014	10.5275	0.000316	0.52448	1.689580123
11	1	0.724556	1.380156	0.322196	11.4847	0.000683	0.572168	1.772104377
12	2	0.342558	5.838427	1.764461	12.6679	0.000442	0.631115	1.879704865
13	4	1.16464	3.434538	1.233882	13.7206	1.01E-03	0.68356	1.980917838
14	1	1.16522	0.858207	-0.15291	14.6242	0.001058	0.728578	2.072131202
15	1	0.552718	1.809241	0.592907	15.4884	0.00063	0.771632	2.16329406
16	3	1.05891	2.833102	1.041372	16.4552	0.000547	0.819798	2.270041388
17	0	0.522124	0	#NUM!	17.2821	0.000386	0.860994	2.365511368
18	1	0.371413	2.692421	0.990441	18.5609	0.000227	0.924704	2.521121994
19	0	0.683458	0	#NUM!	19.6201	3.69E-04	0.977473	2.657732676
20	0	0.009871	0	#NUM!	20.33	4.22E-06	1.012841	2.753411257
21	1	0.247502	4.040371	1.396337	21.4719	2.77E-04	1.06973	2.914592623
22			#DIV/0!	#DIV/0!			0	1
23	1	0.114744	8.715053	2.165052	23.4116	0.000242	1.166366	3.210304884
24	0	0.048203	0	#NUM!	24.5085	5.96E-05	1.221013	3.390622287
25	0	0.111502	0	#NUM!	25.079	1.00E-04	1.249436	3.488374192
26			#DIV/0!	#DIV/0!			0	1
27			#DIV/0!	#DIV/0!			0	1
28	0	0.056783	0	#NUM!	28.2505	5.30E-05	1.40744	4.085482801
29			#DIV/0!	#DIV/0!			0	1
>=30	2	0.561374	3.562687	1.270515	33.0277	0.000457	1.64544	5.183290125

Table 2. Collapsing Empty Dose categories

Dose Catg.	obs	expected	obs/exp	ln(obs/exp)	mean dose	pyrs	fitted value	exp(fitted)
0	593	598.895	0.990157	-0.009892	0	3.87873	0	1
>0	206	201.233	1.023689	0.023413	0.408135	0.302217	0.020333	1.020541
>=1	11	21.8892	0.502531	-0.688098	1.25842	0.016591	0.062694	1.064702
>=2	18	16.9213	1.063748	0.061799	2.64477	0.018896	0.131762	1.140837
>=3	7	8.31737	0.841612	-0.172436	3.27643	0.008574	0.163232	1.177309
>=4	10	7.64965	1.307249	0.267925	4.64366	0.007902	0.231347	1.260297
>=5	3	4.24966	0.705939	-0.348227	5.23644	0.004378	0.260879	1.298071
>=6	4	5.64465	0.708636	-0.344414	6.66942	0.004919	0.332271	1.39413
>=7	6	2.82626	2.122947	0.752805	7.26453	0.002558	0.361919	1.436082
>=8	2	2.31038	0.865658	-0.144265	8.66639	0.002262	0.43176	1.539965
>=9	1	0.9576	1.044277	0.043325	9.25226	0.000963	0.460948	1.585576
10	1	0.3712	2.693966	0.991014	10.5275	0.000316	0.52448	1.68958
11	1	0.724556	1.380156	0.322196	11.4847	0.000683	0.572168	1.772104
12	2	0.342558	5.838427	1.764461	12.6679	0.000442	0.631115	1.879705
13	4	1.16464	3.434538	1.233882	13.7206	0.001013	0.68356	1.980918
14	1	1.16522	0.858207	-0.15291	14.6242	0.001058	0.728578	2.072131
15	1	0.552718	1.809241	0.592907	15.4884	0.00063	0.771632	2.163294
16	3	1.581034	1.897492	0.640533	16.79756	9.33E-04	0.836855	2.309092
17								
18	1	1.054871	0.947983	-0.053418	19.21644	5.97E-04	0.957363	2.604818
19								
20								
21	1	0.257373	3.885412	1.357229	21.4548	2.82E-04	1.068878	2.912111
22								
23	1	0.274449	3.643666	1.29299	23.98907	4.02E-04	1.195136	3.304006
24								
25								
26								
27								
28								
29	2	0.618157	3.235424	1.17416	32.53102	4.57E-04	1.620695	5.056606
>=30								

Appendix 2. Poisson versus Proportional Hazards Regression Approaches

We conducted our analyses using Poisson regression methods. In contrast to proportional hazards regression methods, Poisson regression requires the categorization of all study factors. Nonethesless, grouped data methods are often preferred for cohort analyses.[125, 138]

One reason is that, given with the inherent limitations of this cohort data (for example, problems of measurement error, and the relatively small number of deaths), grouping of data by study factors, after evaluating the data, is unlikely to lead to substantial loss of information. Grouping data does, however, simplify the large amount of individual data into a form more conducive to statistical evaluation. Furthermore, creating tables of person-time facilitates the calculation of disease rates within cells of cross-classified study factors. Examination of the data for trends allows comparison of excess risk and relative risk assumptions, and trends in rates across categories of age and other study factors.

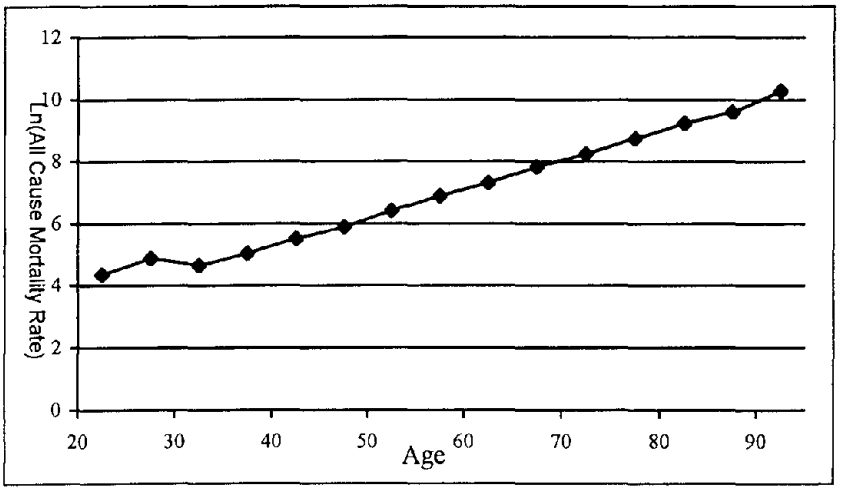
In these analyses we have used the mean value of continuous variables for each cell of the person time table. The use of cell-specific mean values minimizes the sensitivity of estimates to category grouping.[135] Our analyses focused on time-dependent weighting of exposures. It is important to examine the distribution of events by level of accumulated dose in order to understand the range of doses over which models are fit. This is not possible using ungrouped methods for regression, unless one subsequently creates person-time tables. Also, tables of person-time simplify the plotting of mortality rates, or observed to expected counts, by levels of exposure to evaluate the fit of different dose-response models. Finally, standardized residuals between observed and fitted numbers of cases can be calculated for each cell, to further evalute the fit of regression models.

Appendix 3. Noncancer and lung cancer deaths by study covariates in the expanded cohort

Age at risk

For non-cancer causes of death, a Gompertz model, in which the log fatality rate increases or decreases linearly with age, was used. In this case, simply the cell-specific mean age minus 55 years. The appropriateness of this assumption was examined by graphing age by ln(risk) for All Cause mortality in Figure 1; for ischemic heart disease (IHD) in Figure 2; for nonmalignant respiratory disease (NRD) in Figure 3.

Figure 1. Graph of Log-linear relation between Age at risk and All Cause Mortality



The fit of Weibull and Gompertz models were compared for all cause mortality, with reference to change in deviance. Change in deviance for Weibull (ln(age/55): = 4855.12
Change in deviance for Gompertz (age-55): = 5038.73

Figure 2. Graph of Log-linear relation between Age at risk and Ischemic heart disease Mortality

Note that there are no heart disease deaths before age 30; so linear term does not fit as well at youngest ages, but fits well for the range of ages where deaths are observed.
The fit of Weibull and Gompertz models were compared for heart disease mortality, with reference to change in deviance. Change in deviance for Weibull (ln(age/55): = 1892.55
Change in deviance for Gompertz (age-55): = 1865.00

Figure 3. Graph of Log-linear relation between Age at risk and Nonmalignant respiratory disease Mortality

Note that there are no deaths before age 40; so linear term does not fit as well at youngest ages, but fits well across range of ages where deaths are observed. The fit of Weibull and

Gompertz models were compared for respiratory disease mortality, with reference to change in deviance. Change in deviance for Weibull (ln(age/55): = 526.01. Change in deviance for Gompertz (age-55): = 524.06. Conclude that a Ln-linear relationship with non-cancer causes of death.

Deaths by Age Group

Age Group	All Cause Deaths	Lung Cancer	IHD	NRD
<25	14	0	0	0
25-30	45	1	0	0
30-35	50	0	4	0
35-40	86	2	10	0
40-45	143	6	34	1
45-50	196	15	52	8
50-55	288	18	85	6
55-60	392	28	126	18
60-65	475	57	158	16
65-70	529	53	174	23
70-75	421	35	146	32
75-80	319	20	102	36
80-85	196	9	49	15
85-90	86	1	27	10
90+	29	0	9	2

Gender

Deaths by Gender

Gender	All Cause	Lung Cancer	IHD	NRD
M	2890	219	913	150
F	379	26	63	17

Race

Deaths by Race

Race	All Cause	Lung Cancer	IHD	NRD
Caucasian	2961	235	906	156
Other	308	10	70	11

Facility

Deaths by Number of Facilities employed

Facility	All Cause Deaths	Lung Cancer	IHD	NRD
one	2576	189	781	135
greater than one	693	56	195	32

change in deviance with inclusion of term = 0.37

Paycode

Deaths by Paycode

Pay	All Cause	Lung Cancer	IHD	NRD
Weekly or other	1706	134	493	91
Hourly	690	67	209	40
Monthly	873	44	274	36

Birth cohort

Deaths by Birth Cohort

Year of Birth	All Cause	Lung Cancer	IHD	NRD
1 1915-25	1017	105	263	35
2 1905-15	985	68	318	77
3 <1905	778	38	306	49
4 1925+	489	34	89	6

Employment Status

Deaths by Employment Status

Employment Status	All Cause	Lung Cancer	IHD	NRD
not active	2733	204	830	159
active	536	41	146	8

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Enclosed is the final report for our research of time-related factors in radiation-cancer dose response relationships at Oak Ridge National Laboratories (ORNL). Also enclosed are three reprints of the paper, 'Creation of person-time data in cohort analyses' which was written during this research.

To facilitate review of our accomplishments, the tasks outlined in our timeline and Specific Aims are described below with reference to the relevant sections of the Report.

Timeline

Update Cohort

Earlier studies of radiation-cancer dose response relationships at ORNL have considered male Caucasians, who worked at least 30 days at ORNL, had not been employed at another DOE facility, and were hired between 1943-1972. A substantial amount of data has been drawn together in order to create an expanded cohort for our analyses (nearly 5800 workers have been added to the study cohort). We have successfully created an analysis file that includes women, non-Caucasians, and workers with employment at other facilities.

Investigate Lag Assumptions

We conducted analyses to investigate the association between external radiation exposure and all cancer mortality under differing latency assumptions (5, 10, and 20 years). Tables 6.2 describes the results of these analyses for the Checkoway cohort; Table 7.1 and 8.1 describe these associations for the expanded cohort.

Below Limit Exposures, Calculating exposure data

We have not conducted analyses using updated dose estimates from ORNL, following the conclusion of ORNL researchers that the dosimetry data did not adequately lead to a reduction in bias.

Model Building

We created stratified tables of person-time and events by sociodemographic and employment variables. These tables aided our decisions about the categorization and inclusion of these variables in our final regression models. Regression model building then proceeded in a step-wise fashion, evaluating the inclusion of analytical factors and interactions between covariates. Chapters 4 and 5 present a detailed description of the development of a regression model for the expanded cohort.

Data Analysis

Methods for the analysis of time-related factors have been developed, and are described in Chapter 3. Chapters 6-8 present results of the application of these methods to the Checkoway cohort of ORNL workers and to the expanded cohort.

Presentations and Articles

Preliminary results were presented as, "Evidence of Increasing Sensitivity to Radiation at Older Ages among Workers at Oak Ridge National Laboratory" at the International Workshop on Radiation Exposures by Nuclear Facilities, Portsmouth, England, 7/96.

Methods for creation of person-time data, which were developed for these analyses were published in the paper, Wood J, Richardson D, Wing S. "A Simple Program to Create Exact Person-Time Data in Cohort Analyses" International Journal of Epidemiology (1997), 26(2): 395-399.

Methods for investigating age at exposure, which were developed for these anlyses will be reported in the paper, Richardson D, Wing S. "Methods for Investigating Age Differences in the Effects of Prolonged Exposures." American Journal of Industrial Medicine (submitted).

Results of analyses of time-related factors among white male cohort of workers will be reported in the paper, Richardson D, Wing S. "Greater Sensitivity to Radiation Exposures at Older Ages among Workers at Oak Ridge National Laboratory: Follow-up through 1990." Lancet (submitted).

An additional publication reporting the results of anlayses of associations between radiation and cause specific mortality among the expanded cohort of workers will be submitted subsequently.

To help locate the results related to the specific aims outlined in the proposal, results will be indicated related to the specific aims listed in our proposal.

1. Document changes over calendar time in the association of external radiation exposure and cancer mortality under standard latency assumptions. The fit of various model forms for this relationship will be evaluated, and will be used to investigate trends in the dose-response relationship in an expanded ORNL cohort.

Changes over calendar time in radiation-cancer associations are presented Chapter 6, section entitled "Period of Followup" (see Figure 6.7). A comparison of the fit of additive relative risk and multiplicative relative risk models for radiation-cancer associations is presented in Chapter 6, section entitled "Additive Relative Risk Models" (see Table 6.10). The results of analyses in Chapter 6 informed our investigation of explanations for previously observed trends in dose response relationships, and our interpretation of results for analyses of the expanded cohort.

2. Investigate critical time periods of exposure by using induction time analyses for the relationship between radiation exposure and all cancer mortality. These analyses employ exposure time-windows that simultaneously consider lag and time-since-exposure, and allow one to control for exposures in other time windows.

Critical time periods of exposure for the association between all cancer mortality and external radiation exposure were investigated in Chapter 6 in the section entitled "Time-windows of Exposure." Time-windows were used to simultaneously investigate lag and time-since exposure.

3. Investigate age-at-exposure as a potential modifier of dose-response estimates. Within time windows, cumulative exposure will be grouped based on the workers' age at exposure (for example, exposures before, and after, age 45).

We conducted a number of analyses of differences in radiation cancer associations by age at exposure. These analyses are presented in Chapters 6-8, and suggest important differences in the effects of radiation exposures for different ages at exposure.

4. Evaluate the impact of below threshold doses on the effects of age and calendar time on patterns of dose-response.

We have not investigated the impact of below threshold doses. Analyses below threshold dose estimates were found to be problematic.

5. Conduct analyses of all cause mortality and specific cancer and noncancer causes of death.

Chapter 8 presents results for lung cancer, breast cancer, leukemia, cardiovascular disease, non-malignant respiratory disease, and external causes of death.

Additional Analyses

As well as analyses designed to investigate those questions outlined in the Specific Aims, we conducted analyses to investigate additional research questions.

In Chapter 6 (section entitled 'Applying Age-specific Weights to Annual Doses') we investigated the use of smoothed functions for weighting annual external radiation doses by age at exposure. We also investigated changes in latency for doses received at younger ages (Chapter 6, section entitled "Modification of Latency by Age at Exposure"). Analyses also examined differences in radiation-cancer associations for workers hired in different historical periods (Chapter 6, section entitled "Hire Cohort").

Sincerely,

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