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Effects of Exposure to External Ionizing Radiation on Cancer Mortality in Nuclear Workers Monitored for Radiation at Rocketdyne/Atomics International

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Background and Methods *A retrospective cohort study was conducted to estimate the effects of low-level exposure to external (penetrating) radiation on cancer mortality among 4,563 workers monitored for external radiation between 1950 and 1993 at a nuclear research and production facility in Southern California.*

Results *Of the 875 deaths that occurred before 1995, 258 were due to cancer as the underlying cause. External comparisons of male subjects with the U.S. white male population indicated that the workers had lower rates of dying from all causes and all cancers, but a higher rate of dying from leukemia. Internal comparisons of workers exposed at different dose levels, using risk-set analyses with adjustment for confounders, demonstrated an increased mortality rate in workers exposed to 200 mSv for hemato- and lymphopoietic cancers and for lung cancer. Mortality rates for total cancers and "radiosensitive" solid cancers increased monotonically with cumulative radiation dose, but no trends were observed for "nonradiosensitive" cancers.*

Conclusions *Despite possible residual confounding and low precision for estimating effects on specific cancers, these findings indicate that chronic, low-level radiation exposure may have more generalized carcinogenic effects than have been observed in most previous investigations. Such effects may have become evident as a result of the relatively long follow-up period in the present study.* Am. J. Ind. Med. 35:21–31, 1999. *© 1999 Wiley-Liss, Inc.*

KEY WORDS: cancer mortality; ionizing radiation; occupational epidemiology; retrospective cohort study; leukemia; lung cancer; nuclear workers

INTRODUCTION

A key unresolved question in the study of human cancer is the magnitude of effect for chronic, low-level exposure to ionizing radiation. Most of what is known about the risks of radiation in humans has been derived from evaluations of human populations exposed to high doses of gamma or x-radiation, such as patients irradiated during medical procedures or A-bomb survivors. It is not clear, however, whether the findings from such research are adequate to address current concerns about potential carcinogenicity in nuclear workers, whose radiation exposures are lower and much more prolonged [National Research Council, 1990]. The present study provides additional evidence focusing on this issue.

Among A-bomb survivors, uncertainty remains whether whole-body doses of less than 200 mSv have increased the risk of cancer. Extrapolation from data on survivors exposed to more than 200 mSv, using a linear no-threshold model to predict effects at lower doses, yields an estimate of the

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relative risk of cancer (excluding leukemias) equal to 0.41% for each 10 mSv increment (90% confidence interval [CI] = 0.32, 0.52%) [Shimizu et al., 1990].

In studies of low-dose external exposures among nuclear workers, however, estimates of the excess relative risk of cancer per 10 mSv have ranged from 0 to 4.94%, depending on characteristics of the cohort studied, models used to estimate risk, and the lag used for measuring cumulative exposure [Cardis et al., 1995; Fraser et al., 1993; Gribbin et al., 1993; Wing et al., 1991]. Thus, results obtained from some nuclear-worker studies raise the possibility that risk estimates for total cancers extrapolated from the A-bomb-survivor data might underestimate the carcinogenic effect of low-dose radiation exposure by as much as 10-fold. Nevertheless, other occupational results are consistent with the hypothesis of no effect at the doses and dose rates studied.

The only type of cancer usually found to be associated with occupational radiation exposure is leukemia [Cardis et al., 1995]; but even for these cancers, effect estimates vary widely across studies, and no effects were found in studies conducted at the Hanford facility and the Y-12 facility at Oakridge [Frome et al., 1997; Gilbert et al., 1989]. On the basis of their pooled analysis of data from seven previously published cohort studies, Cardis et al. [1995] concluded that there seems to be no effect of occupational exposure to low-level ionizing radiation on cancers other than leukemias. Although pooling data from multiple studies decreases random error in estimating the overall effect, it may obscure differences among studies. The nuclear cohorts studied to date have varied with respect to radiation types and dose rates, the lag in exposure measurement, and duration of follow-up. In addition, errors in measuring exposures or outcomes, healthy-worker selection biases, residual confounding due to unmeasured risk factors such as smoking and chemical exposures, and different distributions of effect modifiers most likely have contributed to the inconsistencies observed across studies. Rather than regarding such heterogeneity across studies as a nuisance factor, the special features and findings of each worker cohort, even smaller ones, may provide important clues if interpreted carefully [Greenland, 1998].

The nuclear-worker study described in this paper analyzes the pattern of cancer deaths associated with low-level exposure to external, penetrating radiation among workers employed since 1950 at the Rocketdyne/Atomics International (AI) Division of Boeing North America, Inc. (formerly Rockwell International). The major sources of external-radiation exposure at Rocketdyne/AI resulted from the operation of nuclear reactors, criticality testing, the manufacture of reactor-fuel assemblies, disassembly of reactors and used-fuel assemblies, small-scale laboratory research, storage of radioactive material, and decontamination and decommissioning activities from 1957 to the early 1990s.

MATERIALS AND METHODS

Study Design and Subject Selection

We drew on the population of all workers employed at Rocketdyne/AI since 1950 (55,000 total registered in the company's personnel files) to carry out a retrospective cohort study of cancer mortality. Personnel and radiation-monitoring records from 1950 through 1993 allowed us to define the study population and to obtain radiation doses and other employee information. Death certificates were retrieved from Rocketdyne/AI pension files, supplemented by state vital-statistics archives.

To minimize exposure misclassification and healthy-worker-selection bias, we restricted our analyses to the 5,066 Rocketdyne/AI workers enrolled in the company's health physics radiation monitoring program between January 1, 1950 and December 31, 1993. We assumed that individuals enrolled in this program were most likely subject to similar self- or company-selection procedures and that monitoring records of different individuals were of comparable quality. The study cohort consisted of those 4,563 enrollees who had been monitored for external radiation exposure at least once during their employment at Rocketdyne/AI. Excluded were 401 workers for whom there were no records indicating whether they had been exposed and another 102 who lacked company personnel records, making it impossible to track their vital status (see Table I). We did not restrict the cohort based on employment duration, race, or gender.

Follow-up for each subject began at the start of monitoring for external radiation exposure or on January 1, 1950, whichever date was later. Follow-up ended either on the date of death or on December 31, 1994, whichever date was first.

Death Certificates

We received 334 death certificates of vested cohort members from the company. If two independent company data sources identified an employee as active at the end of follow-up, we counted that worker as alive. About 10% of the cohort were identified as alive on the basis of this method.

Employees not identified as alive or dead by company records were checked against three different record systems: the Social Security Administration (SSA) beneficiary-records files (period covered: 1935–1994), the vital-statistics files for the State of California (period covered: 1960–1994), and the U.S. National Death Index (NDI) (period covered: 1979–1994). Matches were verified from a review of information on death certificates. From all sources com-

TABLE I. Characteristics of the Study Cohort of Nuclear Workers Monitored for Radiation at Rocketdyne/Atomics International 1950–1993, by Gender

	Male	Female	Total (%)
Number of employees	4,289	274	4,563
Average follow-up time (years)	26.1	25.5	26.1
Average age at entry into cohort (years)	34.1	31.2	33.9
Number of person years	111,765	6,984	118,749
Number of deaths	844	31	875
Total mortality rate (per 10^5/year)	755	444	737
Total cancer mortality rate (per 10^5/year)	222	143	217
Pay type			
Salaried managerial/professional	1,474	57	1,531 (33.6)
Salaried technical/administrative	355	152	507 (11.1)
Hourly/union	2,258	56	2,314 (50.7)
Unknown	202	9	211 (4.6)
External radiation dose (mSv)			
0	532	46	578 (12.7)
1–<5	2,007	164	2,171 (47.6)
5–<10	616	26	642 (14.1)
10–<20	572	17	589 (12.9)
20–<50	326	11	337 (7.4)
50–<100	147	9	156 (3.4)
100–<200	55	1	56 (1.2)
≥200	34	0	34 (0.7)

bined, we identified 875 subjects who died between 1959 and 1994. We were able to obtain all but 30 of their death certificates. At least seven of the 30 might be missing because the deaths occurred outside the United States, which would preclude any death certificate being filed with the NDI. Used together, the three computerized death-identification systems and the Rocketdyne/AI files were comprehensive enough to justify designating any person as alive at the end of follow-up if not identified as dead by at least one of these systems. In a reliability check that we performed, the NDI correctly identified 97.8% (all but one) of the deaths from a 10% sample of known deaths.

A licensed nosologist coded the cause-of-death information recorded on each death certificate using the 9th revision of the International Classification of Diseases (ICD-9) [U.S. Department of Health and Human Services, 1989, 1991]. Both the underlying and associated (contributing) causes were coded; however, the analyses presented here will include underlying causes only. The coding was checked for accuracy, and discrepancies were discussed and reconciled by two members of the study team. For certain analyses (external comparisons, see below), ICD-9 codes were translated into codes of the 8th revision (ICDA-8) (see Table II).

Radiation Records

Most external-radiation monitoring at Rocketdyne/AI involved whole-body doses of gamma rays and X rays. Records also contain readings of exposure to beta-radiation and neutrons. ''Cumulative dose'' in this paper includes penetrating or deep exposures, but excludes superficial skin doses and doses to the hands or feet alone. Neutron exposures have been excluded from the study, since they contributed only a small fraction of the total dose to individual and population doses, and since their inclusion raises uncertainties as to the appropriate quality factor [Kathren and Peterson, 1989].

Dose measures were taken from film badges, thermoluminescent dosimeters, or pocket-chamber dosimeters. During some periods, readings were taken by more than one device, usually a film-badge and a pocket dosimeter. Film-badge readings were given preference over pocket-dosimeter readings since the badges provide greater accuracy of measurement.

Our exposure estimates include doses received by workers at all Rocketdyne/AI facilities. Pre-Rocketdyne/AI exposures were excluded from most analyses because it is not known how consistently and accurately they were reported to and recorded by Rocketdyne/AI. Information about radiation doses received during subsequent employment at other nuclear facilities was not available.

In the total cohort of workers monitored for external exposure, 2,253 were also monitored for internal exposure to radionuclides. More than 90% of the internal-exposure records reported urinalysis measurements of either uranium or mixed-fission products. A time-weighted-average internal dose for each individual was calculated for each year of monitoring [Crawford-Brown et al., 1989; International Commission on Radiological Protection, 1978, 1980, 1987]. For analyses presented in this paper, we attributed an internal-radiation dose of 0 mSv to all workers never monitored for internal radiation.

Personnel and Medical Records

Potential confounders could be assessed through several types of information included in the records. From personnel files, workers were assigned to one of three pay-type categories (hourly/union, salaried technical/administrative, or managerial/professional); this variable was used as a proxy for socioeconomic status. Employees who changed titles or pay type were categorized according to the titles and pay types held longest at Rocketdyne/AI. The 211 subjects lacking job titles and pay type were assigned to the hourly category.

Since Rocketdyne/AI did not systematically collect data on the race of its employees before 1972, we were unable to

TABLE II. Observed (Obs), and Expected (Exp) Numbers of Deaths for White Male Monitored Nuclear Workers and Estimated SMR: Comparison with the U.S. Population, by Underlying Cause of Death

Causes of death	Obs no.	Exp. no.	SMR	(95% CI)
All causes (ICDA-8 001-998)	844	1,238.02	0.68	(0.64–0.73)
All cancers (ICDA-8 140-229)	248	314.82	0.79	(0.69–0.89)
Cancers				
Buccal cavity and pharynx (ICDA-8 140-149)	6	8.24	0.73	(0.27–1.58)
Digestive organs and peritoneum (ICDA-8 150-159)	67	75.90	0.88	(0.68–1.12)
Esophagus (ICDA-8 150)	8	7.89	1.01	(0.44–2.00)
Stomach (ICDA-8 151)	11	10.53	1.04	(0.52–1.87)
Large intestines (ICDA-8 153)	26	28.11	0.92	(0.60–1.36)
Rectum (ICDA-8 154)	4	6.07	0.66	(0.18–1.69)
Liver (ICDA-8 155-156)	2	5.00	0.40	(0.04–1.44)
Pancreas (ICDA-8 157)	15	15.41	0.97	(0.54–1.61)
Respiratory system (ICDA-8 160-163)	91	121.86	0.75	(0.60–0.92)
Larynx (ICDA-8 161)	4	4.11	0.97	(0.26–2.49)
Lung, primary and secondary (ICDA-8 162)	87	116.57	0.75	(0.60–0.92)
Bone (ICDA-8 170)	0	0.80	0.00	
Skin (ICDA-8 172-173)	6	7.01	0.86	(0.31–1.86)
Prostate (ICDA-8 185)	14	20.71	0.68	(0.37–1.13)
Testis (ICDA-8 186-187)	1	1.16	0.86	(0.01–4.78)
Bladder (ICDA-8 188)	4	7.15	0.56	(0.15–1.43)
Kidney (ICDA-8 189)	8	8.12	0.99	(0.42–1.94)
Eye (ICDA-8 190)	0	0.19	0.00	
Brain and other central nervous system (ICDA-8 191-192)	11	9.27	1.19	(0.59–2.12)
Thyroid (ICDA-8 193)	0	0.53	0.00	
Lymphosarcoma and reticulosarcoma (ICDA-8 200)	2	3.72	0.54	(0.06–1.94)
Hodgkin's disease (ICDA-8 201)	2	2.23	0.90	(0.10–3.23)
Leukemia and aleukemia (ICDA-8 204-207)	18	11.28	1.60	(0.95–2.52)
Lymphatic tissue (ICDA-8 202-203, 208)	8	11.71	0.68	(0.29–1.34)
Lymphopoietic cancer (ICDA-8 200-208)	30	29.68	1.01	(0.68–1.44)
Cancer residual[a]	10	24.15	0.41	
Other causes				
Benign neoplasms (ICDA-8 210)	1	3.13	0.32	(0.00–1.78)
Diseases of blood and blood-forming organs (ICDA-8 280-89)	2	2.65	0.75	(0.08–2.73)
All diseases of circulatory system (ICDA-8 390-458)	356	563.74	0.63	(0.57–0.70)
Arteriosclerotic heart disease, including CHD (ICDA-8 410-14)	223	399.70	0.56	(0.49–0.64)
All vascular lesions of CNS (ICDA-8 430-438)	33	57.41	0.57	(0.40–0.81)
All respiratory diseases (ICDA-8 460-519)	48	85.60	0.56	(0.41–0.74)
Emphysema (ICDA-8 492)	8	13.06	0.61	(0.26–1.21)
All diseases of digestive system (ICDA-8 520-577)	25	58.83	0.42	(0.27–0.63)
Cirrhosis of liver (ICDA-8 571)	15	33.18	0.45	(0.25–0.75)
All diseases of genito-urinary system (ICDA-8 580-629)	13	13.97	0.93	(0.49–1.59)
All external causes of death (ICDA-8 800-998)	74	111.83	0.66	(0.52–0.83)
Suicide (ICDA-8 950-959)	24	29.46	0.81	(0.52–1.21)
Total residual[b]	32	2.58	12.41	

[a]Cancers of unspecified site.
[b]Including undetermined causes of death and missing causes of deaths due to missing death certificates.

control for the influence of this factor in our analyses. According to the information on death certificates, however, 96% of all deceased workers were white.

Job titles, employment periods, and, when available, job locations were used to create proxy measures of chemical exposures during the study period. We determined that

hydrazine, asbestos, beryllium, and many solvents had been used extensively at Rocketdyne/AI. We identified two main locations where workers holding the job titles ''mechanic,'' ''engineer,'' and ''machinist'' were exposed to asbestos from insulation work. Hydrazine exposure was likely to occur among mechanics who were transferred to the rocket-engine test-stand facilities of Rocketdyne/AI. On the basis of such considerations, workers were assigned to four categories of presumptive asbestos and hydrazine exposures: high, medium, low, and unexposed.

Information about tobacco smoking was systematically recorded for two subgroups of subjects in routinely administered medical questionnaires from different periods. Questionnaires from 1961 to 1969 indicated only whether the worker was a smoker; after 1980, the level of smoking and dates of starting and quitting were specified. Since smoking information was not available for most of the study population, we examined the association between smoking status and cumulative radiation dose in those workers for whom smoking information was available (1,096 subjects) to assess potential confounding in the larger cohort. We also compared the smoking prevalence in those 1,096 workers with the smoking prevalence in the U.S. male population during the same periods.

Statistical Methods

Two analytic approaches were used in this study for different purposes: (1) external comparisons of our monitored workers with the general U.S. population to assess healthy-worker effects; and (2) internal comparisons among monitored workers according to measured dose levels of radiation exposure (dose-response analyses) to estimate radiation effects.

In external comparisons, the Monson [1994] program was used to estimate standardized mortality ratios (SMRs = observed/expected deaths) for the monitored study population. Expected numbers of deaths were estimated from the mortality rates of the U.S. white male population, stratified by age (5-year categories) and calendar year (5-year intervals). Estimation of 95% confidence limits for the SMRs was based on a formula derived by Byar and recommended by Breslow and Day [1987].

For many types of cancer, our cohort yielded 10 or fewer deaths, too few for meaningful dose-response analyses. Because of this limitation, the outcomes examined in the internal comparisons were restricted to deaths from all cancers, lung cancer (ICD-9 162), and two groups of cancers for which BEIR V presented evidence of radiation sensitivity [National Research Council, 1990]: (1) hemato- and lymphopoietic cancers (ICD-9 200–208, excluding chronic lymphocytic leukemias), which were further divided into leukemias (ICD-9 204–208) and lymphomas or multiple myelomas (ICD-9 200–203); and (2) solid cancers, including cancers of the lung (ICD-9 162), esophagus (ICD-9 150), stomach (ICD-9 151), colon (ICD-9 153), brain (ICD-9 191–192), breast (ICD-9 174), and urinary-tract system (ICD-9 188–189). We did not observe any deaths from cancers of the bone, ovaries, and thyroid in our study population. In addition, we estimated the effect of radiation on death from those solid cancers that BEIR V did not consider to be radiosensitive [National Research Council, 1990].

For internal comparisons, we employed the risk-set approach for cohort analysis described by Breslow and Day [1987]. In this approach, conditional logistic regression is used to compare individuals who have died of cancer with individuals still at risk of dying from cancer (survivors). We constructed risk sets of deaths and survivors for use in the analysis by matching to each cancer death all cohort members who were still alive at the calendar time of the index subject's death. This procedure provided us with an average of 3,578 survivors for each cancer death.

We believe that the small size of our cohort and the narrow range of RRs made it impossible to decide whether a linear or loglinear model fits our data better. We decided to employ a loglinear multiplicative model, rather than a linear model, since the former model has somewhat better statistical properties in small samples, particularly with highly skewed exposure distributions, and it is more likely to converge [Breslow and Day, 1987]. We modeled cumulative radiation dose both as a set of binary variables and as a continuous variable (in mSv). Using cutpoints established in previous studies, we categorized dose equivalents for external penetrating radiation into four ordinal levels: $<$10 mSv, 10-$<$20 mSv, 20-$<$200 mSv, and $\geq$200 mSv. To allow for a period of cancer induction/latency after exposure to radiation and to deal with possible selection bias [Arrighi and Hertz-Picciotto, 1995], we lagged cumulative doses by 0, 2, 5, 10, 15, and 20 years. Lagging was achieved by limiting the cumulative dose for each individual in a risk set to the dose received 0, 2, 5, 10, 15, and 20 years before the index death.

Results of the conditional logistic regression analyses were used to estimate rate ratios and 95% confidence intervals (CI) for the effects of external radiation and other covariates in the model. All *P* values reported in this paper are based on two-sided tests. To test for a monotonic trend in the association between cumulative-dose category and cancer mortality, the means of each of the four dose categories were used as exposure scores. The model allowed us to use individual doses and to treat dose and some other variables, such as time since first monitoring, as time dependent.

In all models, we explored the influence of potential confounders. Only selected models will be presented here. A covariate remained in the model if its presence changed the estimated rate ratio for radiation exposure by more than 10% for any outcome considered [see Greenland, 1989]. All models incorporated adjustment for the same covariates, even if a covariate did not meet our change-in-estimate

TABLE III. Adjusted Rate-Ratio (RR) Estimates (and 95% CI) for the Effect of Cumulative External Radiation Dose and Other Predictors on Cancer Mortality for All Cohort Members of Rocketdyne/Atomics International, Monitored for External Radiation, by Cancer Type, Assuming Zero Lag for Exposure: Results of Conditional Logistic Regression Analyses

Predictor variable	All cancers	Hemato- and lymphopoietic cancers[a]	Lung cancer[b]	Radiosensitive solid cancers[c]	Non-radiosensitive solid cancers[d]
Age at risk[e,f]	1.10 (1.09–1.12)	1.09 (1.05–1.13)	1.10 (1.08–1.12)	1.10 (1.09–1.12)	1.11 (1.09–1.14)
Time since first monitored[e,f]	0.99 (0.97–1.01)	1.06 (0.98–1.15)	0.98 (0.95–1.01)	0.98 (0.96–1.01)	0.98 (0.95–1.02)
Pay type: salaried managerial/professional vs. other	0.76 (0.58–1.00)	1.27 (0.58–2.79)	0.48 (0.28–0.81)	0.76 (0.54–1.07)	0.60 (0.35–1.04)
Internal radiation dose[f,g]	1.03 (0.89–1.21)	1.16 (0.91–1.47)	0.78 (0.35–1.74)	1.00 (0.78–1.28)	1.01 (0.74–1.38)

External Radiation dose (mSv)[e]	No. cancer deaths		No. cancer deaths		No. cancer deaths		No. cancer deaths		No. cancer deaths	
<10	177	1.00	15	1.00	65	1.00	111	1.00	51	1.00
10–<20	41	1.07 (0.75–1.52)	7	1.74 (0.68–4.45)	8	0.63 (0.30–1.33)	21	0.90 (0.56–1.45)	13	1.21 (0.64–2.27)
20–<200	36	1.13 (0.78–1.65)	4	1.00 (0.31–3.21)	12	1.18 (0.61–2.28)	24	1.24 (0.78–1.98)	8	0.93 (0.43–2.03)
≥200	4	3.10 (1.13–8.48)	2	15.65 (3.33–73.5)	2	4.70 (1.05–21.0)	2	2.55 (0.62–10.5)	0	
P for trend[h]		0.036		0.003		0.045		0.12		0.58

[a]ICD-9 200-208, excluding chronic lymphatic leukemia.
[b]ICD-9 162. Note: lung cancers are a subgroup of the radiosensitive cancers.
[c]ICD-9 150, 151, 153, 162, 174, 188, 189, 191, 192.
[d]ICD-9 140-149, 152, 154-161, 163-173, 175-187, 190, 193-199.
[e]Measured in one-year increments.
[f]Treated as time-dependent.
[g]Assumes lung doses due to radionuclide exposures are equal to zero for employees not monitored for internal radiation; internal dose is measured in 10 mSv increments.
[h]The two-sided test for trend was performed by entering an interval variable with the category means as the score values into the logistic regression model.

criterion for all outcomes. The covariates included in all models were pay type, time since first monitoring, age at risk (continuous), and internal-radiation dose (continuous). We treated age and internal-radiation dose as continuous to enhance efficiency, since analyses based on age or dose categories suggested approximate log-linear relationships with cancer mortality. Time since first monitoring was used to control for the selective loss of less healthy workers [Flanders et al., 1989]. Gender, asbestos exposure, and hydrazine exposure were excluded from the analyses presented here because they did not change the estimated radiation effects by more than 10% for any outcome.

RESULTS

Our cohort was characterized by a long follow-up period (average 26.1 years) and a high percentage of salaried employees (44.6%) (see Table I). Only 2% of the monitored workers received cumulative external-radiation doses in excess of 100 mSv, and three-quarters of the workers had recorded doses below 10 mSv.

During the study period, 875 (19.2%) subjects died. We observed 248 cancer deaths among males and 10 cancer deaths among females, yielding a total cancer-mortality rate of 217 per 100,000/year (Table I). Mortality rates for all causes and for all cancers were markedly lower among male workers monitored for external exposure than among U.S. white males (Table II). The only cause of death with an estimated SMR greater than 1.2 was leukemia (SMR = 1.6; 95% CI = 0.95, 2.52). A marked deficit was observed for deaths from diseases of the circulatory system (SMR = 0.63; 95% CI = 0.57, 0.70).

With a zero lag in exposure measurement, total-cancer mortality was found to increase monotonically with cumulative radiation dose (P for trend = 0.036). A somewhat weaker trend was observed for all radiosensitive solid cancers (P for trend = 0.12), but no trend was observed for other solid cancers (P = 0.58) (see Table III). Similar results were observed when cumulative radiation dose was lagged by 2–20 years (results not shown). When we excluded lung cancers from the radiosensitive-cancer category no cases

TABLE IV. Adjusted Rate-Ratio (RR) Estimates, 95% CI, and Likelihood Ratiom (LR) χ^2_{5df} for the Effect of 100 mSv External Radiation Dose on Cancer Mortality Among All Cohort Members of Rocketdyne/Atomics International Monitored for External Radiation, by Exposure Lag and Type of Cancer Outcome: Results From Conditional Logistic Regression Analyses, Where Dose Is Treated as a Continuous Variable*

Outcome	No. of cancer deaths	RR (95% CI) LRχ^2_{5df} [a]	Exposure lag (in years) 0	2	5	10	15	20
All cancers	258	1.17	1.22	1.24	1.22	1.23	1.30	1.33
		(0.93–1.48)	(0.86–1.73)	(0.88–1.76)	(0.85–1.76)	(0.84–1.82)	(0.86–1.96)	(0.83–2.15)
		294.86	294.45	294.65	294.35	294.31	294.66	294.50
Hemato- and lymphopoietic cancers[b]	28	1.42	1.99	2.03	2.09	2.28	2.50	2.68
		(0.94–2.14)	(1.17–3.40)	(1.19–3.46)	(1.23–3.57)	(1.34–3.88)	(1.46–4.29)	(1.43–5.03)
		34.65	36.76	36.93	37.23	38.16	38.96	37.99
Lung cancer[c]	87	1.47	1.52	1.55	1.47	1.35	1.34	1.15
		(1.11–1.95)	(0.90–2.55)	(0.92–2.60)	(0.84–2.58)	(0.70–2.62)	(0.64–2.81)	(0.42–3.15)
		106.44	103.79	103.96	103.30	102.57	102.40	101.96
Radiosensitive solid cancers[d]	158	1.26	1.25	1.27	1.22	1.17	1.19	1.22
		(0.98–1.62)	(0.80–1.94)	(0.81–1.97)	(0.76–1.96)	(0.69–1.99)	(0.67–2.13)	(0.63–2.39)
		174.56	172.98	173.10	172.75	172.47	172.48	172.47
Nonradiosensitive solid cancers[e]	72	0.34	0.41	0.42	0.39	0.37	0.39	0.39
		(0.07–1.55)	(0.09–1.87)	(0.09–1.91)	(0.08–1.90)	(0.07–2.01)	(0.07–2.26)	(0.06–2.67)
		101.47	100.14	100.02	100.23	100.13	99.78	99.47

*Adjusted for age-at-risk, pay type (salaried managerial/professional vs. other), internal dose (continuous), and time since first monitored. LR χ^2_{5df} = likelihood ratio chi-square for the model containing external dose (continuous) and four other variables, 95% CI = 95% confidence interval.

[a]This first column describes the results from models in which external radiation dose received previous to employment at Rocketdyne/AI was added to the dose received at Rocketdyne/AI and a lag of zero years was assumed.

[b]ICD-9 200–208 excluding chronic lymphatic leukemia.

[c]ICD-9 162.

[d]ICD-9 150, 151, 153, 162, 174, 188, 189, 191, 192, according to BEIR V, see text.

[e]ICD-9 140–149, 152, 154–161, 163–173, 175–187, 190, 193–199.

were observed at the highest dose level (≥200 mSv). The 71 radiosensitive cancers (excluding lung), however, contributed to the estimates for radiosensitive solid cancers presented in Table III at medium dose levels (for 10-<20 mSv RR = 1.26; 95% CI = 0.67, 2.40; for 20-<200 mSv RR = 1.34; 95% CI = 0.70, 2.70).

We did not observe a monotonic increase in mortality with increasing exposure for either hemato- and lymphopoietic cancers or lung cancers. Because there were relatively few deaths from any specific cancer type, the confidence intervals for the rate ratios associated with exposure categories below 200 mSv were wide and overlapping. Thus, our data are not informative enough to distinguish between a non-monotonic, a linear, or other type of monotonic dose-response relationship. A clearly elevated mortality rate from hemato- and lymphopoietic cancers was found in the highest exposure category (≥200 mSv). Although this finding was based on only two deaths, the *P* value for testing an overall trend was 0.003. Workers exposed to ≥200 mSv also experienced a markedly increased rate of death from lung cancer. The results did not change appreciably for any outcome when associated causes of deaths were added to the underlying causes (results not shown). The estimated rate ratio for the effect of 100 mSv, treating cumulative radiation dose as continuous, was 1.76 (95% CI = 0.71, 4.31) for 13 leukemia deaths and 2.27 (95% CI = 1.18, 4.39) for 15 lymphoma/multiple-myeloma deaths. Given the similarity of the effect estimates for lymphomas and leukemias, combining these cancers into one outcome, as in Tables III and IV, seems justified.

We modeled exposure as a continuous variable to determine how the effects of 100 mSv of external radiation would vary with lags ranging from zero to 20 years (Table IV). The rate-ratio estimates for lung cancers decreased with increasing lag greater than 2 years, while the estimates for hemato- and lymphopoietic cancers and for all cancers increased with increasing lag. The estimates for radiosensitive solid cancers did not change much with different lags. The widths of the confidence intervals around the estimates also increased with increasing lag, due to the decline in the number of observed deaths at higher dose levels. The likelihood ratio chi-square statistic was rather uniform for almost all lags, making it difficult to identify a ''best-fitting'' model on this basis.

Adding previous occupational radiation exposures to the cumulative dose received at Rocketdyne/AI changed

TABLE V. Smoking Prevalence for Externally Monitored Workers Who Were Included in Two Medical Surveys Containing Questions About Smoking, by Cumulative External Radiation Dose Level (mSv) and Period

	1961–1969[a]			1983–1992[b]			
External radiation dose level (mSv)	No. (%) smokers	No. (%) non-smokers	Total (%)	No. (%) smokers	No. (%) ex-smokers	No. (%) non-smokers	Total (%)
<10	360 (63.0)	210 (37.0)	570 (100)	82 (32.3)	84 (33.1)	88 (34.6)	254 (100)
10–<50	91 (65.5)	48 (34.5)	139 (100)	23 (39.7)	22 (37.9)	13 (22.4)	58 (100)
≥50	23 (62.2)	14 (37.8)	37 (100)	5 (22.7)	12 (54.5)	5 (22.7)	22 (100)
Total	474 (63.5)	272 (36.5)	746 (100)	110 (32.9)	118 (35.4)	106 (31.2)	334 (100)

[a]In 1965, 51.3% of the U.S. white male population over the age of 20 were cigarette smokers. However, 60.1% of white males 25–34 years of age were smokers (the mean age of the 746 Rockwell employees included was 31.2 years at the time smoking information was obtained) [U.S. Department of Health, Education, and Welfare, 1979].
[b]In 1980, 37.1% of the U.S. white male population over the age of 20 were cigarette smokers, 31.9% had quit smoking [U.S. Department of Health and Human Services, 1983]. In 1992, 28.6% of the U.S. white male population over the age of 18 were current cigarette smokers [U.S. Department of Health and Human Services, 1992].

rate-ratio estimates only minimally in models with a zero lag, except for a modest shift in the effect estimate for hemato- and lymphopoietic cancers (Table IV, column 2). Inclusion of chemical-exposure measures in the models had little influence on estimated radiation effects. In none of our models did the addition of any product terms between radiation dose and the other covariates yield a *P* value less than 0.15.

Although we could not adjust for smoking as a potential confounder in our models, examination of the subgroup for which smoking data were available demonstrated that smoking prevalence during the 1960s and after 1980 was not associated with cumulative radiation dose (Table V). Moreover, the observed prevalence of smoking in our male subjects was similar to the smoking prevalence of the U.S. male population during the same periods [U.S. Department of Health and Welfare, 1979; U.S. Department of Health and Human Services, 1983, 1992].

DISCUSSION

The possible carcinogenic effects of low-level radiation doses characteristic of occupational exposures have been difficult to assess. The field has been plagued by many inconsistencies across studies with respect to what levels increase risk and which cancer sites are involved. Some investigations of nuclear workers have found increased risks for cancers of the radiosensitive category only (e.g., lung, leukemia, and brain) [Checkoway et al., 1988; Frome et al., 1997; Wiggs et al., 1994; Wilkinson et al., 1987], while others have also implicated cancers not generally considered radiosensitive (e.g., prostate and female genital organs) [Beral et al., 1985; Gilbert et al., 1989]. As mentioned earlier, the authors of a pooled analysis based on seven previously published nuclear-cohort studies concluded that there is no evidence for an effect of low-level ionizing radiation on cancers other than leukemias [Cardis et al., 1995]. Although those researchers mentioned that the reported effect of radiation on leukemias did not differ significantly across studies, the estimated rate ratio associated with a 100 mSv cumulative dose varied between 0.9 and 5.8. Such variation in estimates is most often attributed to random variation, but might also be due to interstudy differences in the distribution of effect modifiers, type of radiation, duration of follow-up, and sources of bias.

To address the implications of healthy-worker selection in our study population, we compared the mortality experience of our cohort with the mortality experience of the U.S. male population. We found that monitored Rocketdyne/AI nuclear workers had lower mortality rates from all causes and from all cancers, as expected. Park et al. [1991] found the mean all-cause SMR (0.79) for employees from nuclear industries to be lower than the corresponding mean SMR (0.83) for all workers; our all-cause SMR (0.68) was even lower. One reason for the strong healthy-worker effect in our study population, similar to that reported for Los Alamos National Laboratory workers [Wiggs et al., 1994], might be the high percentage of college-educated employees in these research facilities. A similar phenomenon is likely to have been a determinant of the lower total-cancer-mortality rate in our cohort, compared with the U.S. male population (SMR = 0.79). Rocketdyne/AI employees historically had extensive health-insurance coverage, which would be expected to reduce the proportion of cancers that were fatal [Demers et al., 1992].

Limited exposure misclassification may have occurred in our study as a result of variation in the frequency with which film badges were changed. Since a film badge will fail to register radiation doses that total less than the minimum detection limit (0.1 mSv at Rocketdyne/AI), the more often film badges were changed, the more likely low-level exposures would escape detection. Thus, film badge readings taken for workers during the early 1950s, when badges were

replaced most frequently, might underestimate the actual dose equivalent received by those employees. On the other hand, during these early years of operation pocket dosimeters were frequently used instead of film badges. Pocket chambers have a tendency to be discharged from sources other than radiation and, thus, their readings tend to overestimate radiation doses. Further errors might have been introduced by variations in recording practices for doses near or below the detection limit and laboratory variation in reading dosimeters. The direction of bias is not easily predictable since it would depend on a combination of factors contributing to measurement error.

As in other studies of nuclear cohorts, death certificates provided the only practical source of information on cancer outcomes. Death certificates alone are not always an accurate indicator of what specific cancer site was the underlying cause of death, and they often fail to list multiple primary cancers in the same individual. Misclassification of any cancer death as a non-cancer death is expected to be nondifferential with respect to radiation and will most likely bias our results for total cancers towards the null. If, however, cancers of radiosensitive sites are misclassified as nonradiosensitive cancers or vice versa, the bias would be downward for one site and upward for the other, depending on the direction of misclassification. Our study was further complicated by the small numbers of many specific cancer types, such that adding or subtracting only one death from a given exposure category could change the results appreciably. This problem was reduced by grouping cancers into broad categories. Although such grouping might also mask differences in effects among specific types of cancer, there was no evidence of such differences when disaggregating hemato- and lymphopoietic cancers into leukemias and lymphomas.

To assess the potentially confounding influence of carcinogenic chemicals used extensively at Rocketdyne/AI, we created proxy measures of asbestos and hydrazine exposures, based on job titles during selected periods of employment and (for asbestos) on selected work locations. None of the radiation effects that we observed changed appreciably when adjusting for these measures. Since no quantitative information was available on individual levels of chemical exposures, however, misclassification may have distorted our control for these confounders. Thus, we cannot rule out residual confounding due to these or other unmeasured risk factors.

We were not able to adjust for smoking, a risk factor for many of the cancers considered in our analyses. However, examination of the smoking-radiation association in subgroups of our study population indicated no systematic variation of smoking behavior across external-radiation-dose levels. A previous case-control study showed that tobacco use was not strongly related to the level of radiation exposure, and that adjustment for smoking in the analysis did not appreciably change the estimated effects of cumulative dose on lung-cancer risk [Petersen et al., 1990]. Nevertheless, residual confounding due to smoking cannot be ruled out entirely, especially with lung cancer.

Our analyses included a range of lags for measuring cumulative radiation dose to deal with possible differences in the periods of induction, latency, and expression (before death) among cancers of different types and with different fatality rates. For total cancers and for hemato- and lymphopoietic cancers, lags of 15 to 20 years yielded the largest rate-ratio estimates. Although it is best to perform lagged analyses with specific cancer sites, in our study there was insufficient information to perform such analyses, except for lung cancer. Checkoway et al. [1988] found that the effect of radiation on lung-cancer mortality diminished with increasing lag in exposure measurement and suggested that this could be interpreted as a predominantly late-stage effect on lung cancer. We observed the same phenomenon (see Table IV). Since neither Checkoway et al. nor our study controlled for the effects of smoking, however, these results should be interpreted with caution.

Most cancers may require a relatively long period (e.g., 10–20 years) to develop after radiation exposure, especially when exposure occurs early in adult life. Employing A-bomb survivor data, Shimizu et al. [1990] and Pierce et al. [1996] saw no evidence that radiation-induced cancers appear earlier than do other cancers at the same sites; instead, the increase in site-specific, radiation-related cancer mortality apparently occurs at approximately the same ages when cancer mortality from background sources increases. They concluded that the pattern of excess risk for solid cancers reflects a life-long elevation of the natural age-specific cancer risk. Findings and conclusions from previous studies in the nuclear industry changed considerably with increasing length of follow-up [e.g., Wilkinson et al., 1987, 1997; Wing et al., 1991]. Thus, the limited length of follow-up in many of the earlier investigations may have limited their ability to detect radiation effects on many types of cancer occurring naturally late in life.

The present study has the relative advantages of one of the longest follow-up periods reported in the literature to date and some attempts to control empirically for smoking and occupational exposure to chemicals. Contrary to the reported findings for several other nuclear cohorts [Cardis et al., 1995] and despite the limited size of our cohort, we found radiation effects not only for blood and lymph cancers, but also for solid radiosensitive cancers. The latter results may be attributable to our extended follow-up. Since only 19% of our cohort had died before 1995, however, follow-up of this population should continue to confirm and expand our findings.

The increase in mortality from hemato- and lymphopoietic cancers that we observed occurred at levels of chronic radiation exposure assumed acceptable under U.S. govern-

ment standards [International Commission on Radiological Protection, 1984]. This result is consistent with the elevated rate of leukemia mortality in the total cohort (relative to the U.S. population), and it is consistent with the effect of external radiation observed in several other occupational studies.

The elevated rate of lung-cancer mortality among workers with at least 200 mSv did not appear to be attributable to confounding by smoking, asbestos, or hydrazine exposures. An association between external radiation and lung-cancer mortality has been reported previously in a few studies of nuclear workers [Beral et al., 1988; Checkoway et al, 1988; Frome et al., 1997], but not in most others [Cardis et al., 1995]. The dose-dependent increase in mortality from radiosensitive solid cancers in our cohort was strongly influenced by the results for lung cancer, which represented 55% of all deaths in that outcome group. The positive trend was not, however, due solely to lung cancer. On the other hand, no association was observed between external-radiation dose and death from cancers *not* classified as ''radiosensitive'' according to BEIR V. In accordance with the results from A-bomb survivor studies [Shimizu et al., 1990; Pierce et al., 1996], we found an effect of ionizing radiation exposure on solid-cancer mortality. Such an effect of low-level radiation on cancers other than leukemias has been described in two previous studies [Kneale and Stewart, 1993; Wing et al., 1991], but was rejected by a recent analysis pooling the data from several nuclear worker cohorts [Cardis et al., 1995]. Despite possible residual confounding and low precision for estimating effects on specific cancers, our results suggest that chronic, low-level radiation exposures may have more generalized carcinogenic effects than have been observed in most previous investigations. Such effects may have become evident as a result of the relatively long follow-up period in our study. Nevertheless, given the inconsistencies across studies in the types of cancers found to be associated with occupational radiation exposure, our results for lung and other solid cancers require confirmation through further follow-up of our study cohort and replication in other populations.

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