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Abstract

STUDIES ON PERSONS EXPOSED TO PLUTONIUM.

The results of four studies of persons exposed, or potentially exposed, to plutonium are summarized. The studies are: 1) a five-year update on clinical examinations and health experience of 26 Manhattan District workers heavily exposed at Los Alamos in 1944-1945; 2) a 30-year mortality follow-up of 224 white male workers with plutonium body burdens of 10 nCi or more; 3) a review of cancer mortality rates between 1950 and 1969 among Los Alamos County, New Mexico, male residents, all of whom have worked in or have lived within a few kilometers of a major plutonium plant and other nuclear facilities; and 4) a review of cancer incidence rates between 1969 and 1974 in male residents of Los Alamos County.

No excess of mortality due to any cause was observed in the 224 male subjects with the highest plutonium exposures at Los Alamos. The total cancer and cardiovascular mortality rates were lower than expected based on age and year-specific rates for United States white males. Lung cancer mortality was lower than expected and no bone or liver cancer was experienced. Clinical examinations of the Manhattan District workers, whose average age in 1976 was 56 years, show them to be active persons with diseases that are not unusual for their ages. The two deaths in this group over the past 30 years have not been due to cancer.

The mortality study of Los Alamos male residents showed a possible excess of cancers of the combined lymphatic and hematopoietic tissues, but the incidence data suggest this excess, if real, is no longer occurring. Higher than expected incidence of cancers of the digestive tract in Los Alamos males and females is more likely due to socioeconomic and cultural factors than to occupational exposures. Mortality and incidence data indicate no excess of lung cancer in Los Alamos males.

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INTRODUCTION

Research and development work on plutonium has played an important role throughout the entire history of Los Alamos, New Mexico. It began during World War II when Los Alamos, the isolated mountain location of a small private boys' school, was selected as the site for the Manhattan Engineer District's laboratory that was to develop the first atomic bomb. One of the tasks for the scientists, technicians, and craftsmen assigned to the Los Alamos project in 1943-45 was to develop methods to process and fabricate the newly discovered element, plutonium. Other workers were engaged in chemistry, physics, and metallurgy research. These workers and their families lived in wartime accommodations located close to the laboratories.

From this unusual beginning, Los Alamos has grown to a community of over 15,000 persons in the 1970s. It is still a one-industry town in which the principal employer is the Los Alamos Scientific Laboratory. Laboratory personnel continue to conduct research in nuclear and particle physics, plasma physics, nuclear chemistry, analytical and physical chemistry, materials science, and many other areas of advanced science and technology. Throughout the years, hundreds of persons have continued to work with transuranic elements, especially plutonium. The community residents have been

closely associated with Laboratory activities, both as employees in the Laboratory and as neighbors. Some residential areas of the town are still located within a few hundred meters of chemical laboratories and radiation areas, including major plutonium facilities. Probably this community has been more intimately associated with the plutonium industry than has any other community.

Since the early 1950s, 26 Los Alamos workers with high plutonium body burdens received in 1944-1945 have been studied clinically for evidence of adverse health effects from internally deposited plutonium. In the 1973 reports on this clinical study [1,2] no medical findings were reported which could be attributed definitely to plutonium. The study of this small group, although providing valuable clinical information, could not provide the extensive information on late health effects that epidemiologic studies can provide. In 1974, we extended our program to include a mortality study of all Los Alamos workers with high body burdens of plutonium as a preliminary effort to provide information on an expanded number of workers.

It was also recognized that the cancer incidence and mortality experience of the population of Los Alamos County might provide useful and important information. This population has lived close enough to the Laboratory facilities to make it useful to attempt to detect potential effects of Laboratory operations, including effects of possible exposures to low environmental levels of chemical or radioactive effluents. Furthermore, as we have seen, a large proportion of the adult population works at the Laboratory and has a potential for occupational exposures to chemicals, radiation, and other hazards. Epidemiologic studies on the Los Alamos County population serve as a screening mechanism for possible health effects.

In this paper we wish to summarize the methods and results of our four studies on plutonium workers and the general population of Los Alamos County.

METHODS AND RESULTS

Clinical Study of Early Los Alamos Plutonium Workers

A group of 26 persons, who had worked with plutonium for the Manhattan Engineer District project at Los Alamos in 1944 and 1945, has been followed with medical examinations periodically since 1953. The subjects were selected for this study based on their exposure history and relatively high plutonium excretion values in urine. The principal mode of exposure was by inhalation. Five of these individuals had contaminated wounds that were excised surgically; only one of these wounds contained a significant amount of plutonium.

Current plutonium body burden estimates on these individuals range from 6 to 230 nCi, or 15 to 575 percent of the 40 nCi maximum permissible body burden for lifetime occupational exposure [3,4]. Eleven persons in the group are estimated currently to have body burdens in excess of 40 nCi.

The latest medical re-examinations of the 24 living subjects in the study were completed in 1976 and 1977. Two deaths have occurred in the group: one in 1959 due to myocardial infarction in a 36 year old male and the second in 1975 in a 50 year old male due to an auto-pedestrian accident.

The latest examinations included complete medical history, physical examination, blood chemistry profiles, hematologic studies, including chromosome analysis of peripheral lymphocytes, sputum cytology, radioanalysis for plutonium in urine, blood, and feces samples, and x-ray studies of the chest, pelvis, femur and teeth. All but two persons were counted with phoswich detectors for plutonium in the chest, liver, and hands and with a large, NaI(Tl) detector for other radionuclides. No unusual radioactivity was found in the 22 subjects, except for 5±2 nCi of plutonium detected in a wound site that was excised in 1944. The two individuals who did not have in vivo measurements made did not travel to Los Alamos for their medical examinations, and the only plutonium measurements on them at this time were made on urine samples.

The mean age of the group in 1976 was 56 years. The current examinations have shown these individuals to be active persons with diseases that are not unusual for their ages. The most significant diagnoses were one case each of coronary heart disease, total blindness due to glaucoma, hypertension with electrocardiographic evidence of left ventricular hypertrophy, and bronchitis and early emphysema in a heavy smoker. The last individual had marked atypia of exfoliated cells in sputum in the 1971-72 studies, but subsequent sputum examinations have shown less severe changes. No subjects were found to have abnormal lung cytology in the latest samples. X-ray evidence of bone changes was discovered in two individuals. Neither individual has had symptoms due to these bone lesions nor have they required treatment. One individual, a 63 year old male with a plutonium body burden above 40 nCi, has slowly progressive Paget's Disease (osteitis deformans) which, in retrospect, can be seen on previous x-rays dating back to 1965. The second individual, 54 years old with a body burden less than 40 nCi, has developed a small area of bone sclerosis in the pelvis since the last x-rays were taken in 1960. These findings are probably not unexpected in a group of this age. For example, x-ray studies show that about 3% of persons over age 40 have Paget's disease; the incidence increases to about 10% of persons in their 80s [5]. It affects men more often than women, and the pelvis is the bone most commonly affected.

Histories of two skin cancers, a localized melanoma of the anterior chest and an epithelioma on the back of the hand, have been noted in the study. Both lesions were treated with local surgical excision over five years ago and neither has recurred. No other cancers have occurred in the group. Three benign tumors have been noted: a hamartoma of the lung, a tumor of the nerve sheath, possibly a neurilemoma, located in the jaw, and a small transient thyroid nodule that is no longer evident.

Mortality Study of 224 Los Alamos Plutonium Workers

A study of the mortality experience of all Los Alamos area plutonium workers with estimated body burdens of 10 nCi or more has been completed. Selection of individuals for this study was done by review of the health physics records at the Los Alamos Scientific Laboratory. All individuals with plutonium burdens equal to or greater than 10 nCi by urine assay as of 1 January 1974 according to the version of the PUQFUA Code [6] then in use were identified. That Code incorporated assumptions that, for the radiological protection of workers, overestimated plutonium body burdens in some cases [7]. An update of that Code is now used which is designed to give an estimate closer to actual deposition values. Had the current version of PUQFUA been in use, the subjects would have been classified only slightly differently but there would have been fewer in the study. Body burdens for the clinical study group discussed above were from the current PUQFUA version.

All 241 Anglo-white[1] and Spanish or Spanish-surnamed subjects were followed, but we report here only on the 224 male subjects, 173 Anglo-white and 51 Spanish. Study subjects were individually followed through 30 June 1976 to determine mortality status. Follow-up was 100% complete through June 1976; there were no untraceable individuals with burdens above 10 nCi despite the thirty-year period of follow-up on most subjects.

Subjects were entered into the study cohort mid-year of the year of their first recorded urine test or of the recorded accident by which they presumably were first exposed. Most subjects would not have received their current or final body burden until some time after entry into the cohort. Because exposure protection was less in earlier years, during and shortly after World War II, and because the great majority of subjects were young when exposed and are only now incurring significant risk of mortality, the precise timing of the major exposure would not significantly affect either observed or expected mortality.

Mortality analysis was carried out using a computer program developed and described by Monson [8]. Age and calendar-year adjusted expected numbers of deaths, based on United States white male rates, were generated and compared to observed numbers of deaths for each cause as coded (ICDA 8) from the death certificates obtained on deceased subjects. Coding of death certificates has not yet been reviewed by an experienced nosologist, but the very few problematic certificates would not significantly affect the conclusions reported in this paper.

Table I describes some characteristics of the cohort of 224 white male plutonium workers and the standardized mortality ratios (SMRs) for broad categories of deaths. Nearly all

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[1] In New Mexico the term, Anglo, is used in some state statistics to designate white persons not of Spanish heritage. There are some differences in disease morbidity and mortality rates between the Anglo-white and Spanish populations in New Mexico.

subjects entered the cohort in the middle or late 1940s, as shown by the average year of entry, 1947.4. The cohort was young at entry, the mean age being 30.9.

The SMR for total mortality was 0.54 ($p<.001$), for all malignant neoplasms 0.64 (not significant), and for diseases of the circulatory system 0.38 ($p<.001$). SMRs for respiratory diseases and external causes were near unity. Results when Anglo-white and Spanish subjects are analyzed separately are consistent with the results presented above.

Cancer is an outcome of special interest in studies of plutonium, and Table II shows observed and expected numbers of cancer for all sites for which a cancer was observed. For no site was there a clear excess; for lung cancer there is an observed deficit. Tests of statistical significance are not useful when observed and expected numbers are this small.

Cancer Mortality In Los Alamos County Male Residents

The portion of the Los Alamos County mortality study reported here concerns only cancer mortality in males. Demographic data are from the 1970 United States Census published in the "City and County Data Book" [9]. Cancer rates are from Mason and McKay's "U.S. Cancer Mortality by County: 1950-1969" [10] and some data on statistical significance are taken from Mason et al.'s "Atlas of Cancer Mortality for U.S. Counties: 1950-1969" [11].

Published cancer rates for white males in Los Alamos County are compared with rates for the State of New Mexico and for the United States. In addition, Los Alamos County white male cancer rates are compared with rates in five socioeconomic and occupational control counties and in five high education Western control counties.

From all U.S. counties with a population above 5000 and a median income rank ≤ 1000, the two counties in the United States most closely bracketing Los Alamos County were selected with respect to four criteria: median education, median family income, percent professional and managerial, and percent government employees. This process, because of correlation among attributes, yields five rather than eight counties: Pitkin, Colorado; Montgomery, Maryland; Mineral, Nevada; Tooele, Utah; and Fairfax, Virginia.

From the remaining counties we selected all Western counties with a median education ≥ 12.8 years for persons aged 25 and above. These were: Marin, California; Boulder, Colorado; Benton, Oregon; Whitman, Washington; and Albany, Wyoming. In this report only summary data for the control counties will be given.

Tests of significance for cancer mortality data are based either on a method given by Chiang [12] for age-adjusted rates or, when small observed numbers are involved, on a method given by Haenszel et al. [13] based on the Poisson distribution.

Table III shows cancer death rates in Los Alamos County white males between 1950 and 1969. The great majority of male residents was employed by one of two Atomic Energy Commission contractors at Los Alamos or by the Atomic Energy

Commission directly. Interpretation is made difficult by the small number of observed and expected deaths. The county population was young in 1950 and has been aging in the same way as the occupational cohort. Mortality due to all cancer was low compared with that in the United States and almost identical to that in the State of New Mexico.

In general, deaths from cancer of the digestive tract were significantly less common in Los Alamos males between 1950 and 1969 than in United States males; only liver cancer did not differ significantly according to Mason and McKay [9]. Lung cancer has been notably and significantly low during this period. Bladder and prostatic cancer have been high but the number of deaths involved is too small to draw any conclusion.

Lymphosarcoma and leukemia have been high, but not statistically significantly high when looked at separately. Because of the respectable number of deaths involved, ten, it was decided to look at all cancer of lymphatic and hematopoietic tissue. A total of 15 were observed: 2 Hodgkin's, 1 lymphosarcoma, 3 multiple myeloma, and 6 leukemia. The total expected was computed from available published data as the sum of: (the observed deaths, for each specific cause) x (U.S. age-adjusted rate)/(Los Alamos County age-adjusted rate). A standardized mortality ratio of 1.63 (15 observed, 9.2 expected) was obtained; by the method of Haenszel [13] the lower limit of its 95% confidence interval is 0.913. The excess of cancers of the lymphatic and hematopoietic tissues is, then, not statistically significant at the 5% level but is a borderline finding.

Cancer mortality rates in Los Alamos County males are also compared with rates in two groups of control counties in Table IV. Results are very similar to those in the previous analysis, but the frequency with which rates in Los Alamos were highest or lowest emphasizes the unique character of the Los Alamos County male population. Again digestive cancer rates were very low, lung cancer was very low, and lymphosarcoma and leukemia were highest. Liver, prostate, and bladder cancer, whose rates are all based on very small numbers, showed the same pattern as previously.

Close control, then, of the socioeconomic characteristics of Los Alamos County does not change the conclusions drawn concerning cancer mortality based on national and state comparisons.

Cancer Incidence in Anglo-white Males, 1969-1974

A study of cancer incidence rates in Los Alamos County residents in recent years supplements the above mortality study. Data on cancer incidence in Los Alamos County were obtained from the New Mexico Tumor Registry of the Cancer Research and Treatment Center at the University of New Mexico. Data are from the registry data base as of October 1976 for the years 1969 through 1974. The data for Anglo-white males are presented in Table V and compared to data from Albuquerque (the largest urban area in New Mexico) and from the entire State of New Mexico for Anglo-white males. Again only small numbers are available for comparison.

Incidence rates for cancers of the digestive tract are high compared to rates in either Albuquerque or the entire state. The standardized morbidity ratio for cancer of the large intestine is 2.35 relative to New Mexico, 2.02 relative to Albuquerque. Lower 95% confidence limits are 1.17 and 1.01 suggesting statistically significantly elevated rates. For all cancer of the digestive tract the corresponding standardized morbidity ratios are 2.33 and 2.02 (lower 95% confidence limits 1.48 and 1.28).

Lung cancer incidence rates were not low, as were mortality rates, but there is no suggestion they were above average during this 1969 to 1974 period. There is also no suggestion that leukemia and lymphoma incidence rates were above average during this period.

DISCUSSION

These studies provide some insight into the incidence and mortality rates of cancer in persons who have lived and worked in close association with the nuclear industry, especially plutonium research and development. The findings on the individuals with highest occupational exposures to plutonium are of special interest. In 26 workers heavily exposed 32 years ago, and followed by periodic medical examinations since 1953, only two cancers, both of the skin, have been recorded. No excess of cancer mortality was noted after a 30 year follow-up period among the 224 white male plutonium workers whose body burdens in 1974 were estimated to be above 10 nCi. Their cardiovascular disease death rates were also notably low. Cancers of bone and liver were absent in these occupational groups and lung cancer was less than expected based on United States white male mortality rates.

Interpretation of cancer mortality and morbidity data on male residents of Los Alamos is complicated by a lack of consistency among some findings. The findings are also based upon small numbers and are thus subject to proportionately large random errors. It should also be noted that incidence rates do not necessarily show the same detailed patterns as mortality rates, especially in the case of cancers with significant five-year survival.

The highly unusual characteristics of Los Alamos community residents could affect expected cancer rates in unpredictable ways. These characteristics include a security clearance required for employment, a high educational level compared even to university communities, a socioeconomic status ranking with the highest counties in the United States, and an isolated nonurban residence. Further, government housing policy linked eligibility for government housing, the only housing available in the county until about 1960, to active employment in the community. This policy could conceivably have led seriously ill persons to move elsewhere; that the policy was never enforced on seriously ill residents was not generally known. Also, because Los Alamos was a newly created community, a tendency for seriously ill persons to return to home communities and be certified at death as residents there might be expected.

No attempt will be made to give all possible explanations for the results presented, but we will set forth a set of hypotheses which seem reasonable to us.

A borderline excess of deaths due to the combined cancers of the lymphatic and hematopoietic tissues did appear in Los Alamos male residents between 1950 and 1969. Neither mortality rates in females from 1950 to 1969 nor incidence rates in males from 1969 to 1974 were high. This suggests that any excess, if real, was probably occupationally induced prior to employment at Los Alamos or during early years when controls of all hazards, including chemicals, in the work place were not up to current standards. Tumors of lymphatic and hematopoietic tissue differ in etiology, and it is not suggested that any one factor could be expected to be responsible. Prior to and during Los Alamos employment some workers could be expected to have been exposed to various hazards of modern technology, including radiation in all its forms and organic and inorganic chemicals.

High incidence rates of cancers of the digestive tract in white males were noted from 1969 to 1974, although mortality due to these cancers was significantly low between 1950 and 1969. Digestive cancer mortality rates in females were significantly high from 1950 through 1969, and the incidence rates in females remained above average from 1969 to 1974. No simple explanation is possible but occupational exposures seem a less likely explanation than socioeconomic and cultural factors, counteracted at first by an exaggerated healthy worker effect. Males were selected for active military service originally, and since 1945 for active employment in a demanding industry and for regional geographic mobility. Females were subject to selection in most cases only by marriage to such males. Both sexes could share the same white-ethnic, social, or behavioral risk factors, counteracted in the males during the first years by the strong healthy worker, healthy migrant, and/or healthy military effects.

It should be noted that neither mortality nor incidence data suggest an excess of cancer of the lung in the male population of Los Alamos County.

Future Studies

While the present study has yielded no evidence of excessive mortality among 224 male plutonium workers, a more extensive study is required. We are currently undertaking a follow-up study of all plutonium workers at Los Alamos; Rocky Flats, Colorado; Mound, Ohio; Savannah River, South Carolina; Hanford, Washington; and Oak Ridge, Tennessee. These plutonium workers, both with and without measurable plutonium burdens, plus unexposed controls will total about 20,000 study subjects.

Case-control studies of individuals with cancer in Los Alamos County since 1950 are also under way. These studies will investigate Los Alamos employment and past job histories, known radiation exposures, neighborhood of residence, and any other factors which can be determined from existing records. We believe these studies will shed needed light on the observations in this paper.

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TABLE I. 30-YEAR MORTALITY IN 224 WHITE MALE PLUTONIUM WORKERS

	Observed	Expected	Obs./Exp.
All causes of death	33	61.3	.54
All malignant neoplasms	7	10.9	.64
All diseases of circulatory system	12	31.8	.38
All respiratory diseases	3	3.3	.92
All external causes	8	6.9	1.16
Other	3	8.4	.36

Average year of entry: 1947.4

Average age of entry: 30.9

Total person-years of survival: 6205

TABLE II. 30-YEAR CANCER MORTALITY IN 224 WHITE MALE PLUTONIUM WORKERS

	Observed	Expected
Buccal cavity and pharynx	1	.39
Stomach	1	.67
Large intestine	1	.96
Rectum	1	.39
Lung	1	3.20
Bladder	1	.31
Lymphosarcoma etc.	1	.29
All digestive organs	3	3.20
All respiratory system	1	3.44
All lymphopoietic	1	1.17

TABLE III. CANCER MORTALITY RATES[a] IN LOS ALAMOS CO., NEW MEXICO, AND UNITED STATES WHITE MALES, 1950-1969

	Los Alamos County		New Mexico	United States	Significance[b] of difference between Los Alamos Co. & U.S. White cancer rates		
	Rate	Cases	Rate	Rate	Direction	Mason & McKay[c]	Poisson[d]
Stomach	3.5	(3)	17.96	15.22	Low	$p<.05$	$p<.05$
Large intestine	8.8	(4)	9.15	16.54	Low	$p<.05$	NS
Rectum	2.8	(2)	3.39	7.65	Low	$p<.05$	NS
Biliary passages & liver	6.3	(2)	5.33	5.16	High	NS	NS
Pancreas	1.0	(1)	8.79	9.63	Low	$p<.05$	$p<.05$
Trachea, bronchus, & lung	12.0	(8)	24.71	37.98	Low	$p<.05$	$p<.05$
Prostate	30.3	(3)	15.87	17.84	High	____[e]	NS
Bladder	15.7	(3)	3.97	6.78	High	NS	NS
Brain and ... nervous system	4.9	(5)	3.30	4.42	High	NS	NS
Lymphosarcoma and reticulosarcoma, etc.	7.1	(4)	3.64	4.89	High	NT	NS
Leukemia	16.3	(6)	7.71	8.81	High	NT	NS
All malignant neoplasms	142.6	(54)	136.30	174.04	Low	NS	NS

[a] Direct age-adjusted average annual rates per 100,000 population, 1950-1969; from "U.S. Cancer Mortality by County: 1950-1969" (Ref. 10).
[b] Two sided probability (p); NS means not significant, NT means not tested.
[c] The 95% confidence intervals for the local and national rates do not overlap; from maps in Reference 11.
[d] Confidence intervals by method of Chiang (Ref. 12).
[e] National rate outside 95% confidence limits for estimate of a Poisson-distributed variable (Ref. 13).
Reference 11 appears to be in error.

TABLE IV. CANCER MORTALITY RATES[a] IN LOS ALAMOS COUNTY AND CONTROL COUNTY WHITE MALES, 1950-1969

	Los Alamos County Rate (Cases)	Socioeconomic control counties (range of five)	High education Western control counties (range of five)	Rank[b] of cancer rates in Los Alamos Co. relative to Socioeconomic & occupational controls (rank n=6)	High education Western controls (rank n=6)	All controls combined (rank n=11)
Stomach	3.5 (3)	7.0 - 13.7	10.9 - 13.8	6	6	11
Large intestine	8.8 (4)	6.4 - 25.5	10.2 - 16.4	5	6	10
Rectum	2.8 (2)	0.0 - 6.5	4.7 - 8.4	5	6	10
Biliary passages & liver	6.3 (2)	0.0 - 4.2	3.7 - 4.3	1	1	1
Pancreas	1.0 (1)	8.9 - 10.5	7.0 - 12.0	6	6	11
Trachea, bronchus, & lung	12.0 (8)	36.8 - 45.0	18.6 - 37.5	6	6	11
Prostate	30.3 (3)	17.2 - 25.8	16.8 - 22.8	1	1	1
Bladder	15.7 (3)	0.0 - 12.7	5.5 - 8.0	1	1	1
Brain and ... nervous system	4.9 (5)	0.0 - 5.8	2.3 - 7.9	2	2	3
Lymphosarcoma & reticulosarcoma, etc.	7.1 (4)	1.6 - 6.0	1.3 - 6.2	1	1	1
Leukemia	16.3 (6)	3.8 - 9.2	9.0 - 11.4	1	1	1
All malignant neoplasms	142.6 (54)	159.4 - 175.0	134.7 - 173.9	6	3	8

[a] Direct age-adjusted average annual rates per 100,000 population, 1950-1969, from "U.S. Cancer Mortality by County: 1950-1969" (Ref. 11).

[b] Rank 1 is highest rate of group, 6 or 11 lowest.

TABLE V. ANGLO WHITE MALE CANCER INCIDENCE RATES IN NEW MEXICO, 1969-1974[a]

Neoplasms	Los Alamos Co. Cases	Los Alamos Co. Rate	Bernalillo Co. (Albuquerque) Rate	New Mexico Rate
Stomach	3	28.4	8.1	8.8
Large intestine	11	60.7	30.0	25.8
Rectum	3	38.2	15.1	11.7
Biliary passages & liver	2	5.7	6.2	5.6
Pancreas	4	29.3	12.5	10.0
Trachea, bronchus, & lung	5	72.4	69.7	63.9
Prostate	6	47.2	80.7	60.0
Bladder	4	61.9	32.2	20.7
Brain and ... nervous system	2	3.7	7.7	6.4
Lymphosarcoma & reticulosarcoma, etc.	3	6.5	6.6	7.1
Leukemia	5	12.7	15.2	13.1
All malignant neoplasms				
Rate		420.2	380.0	311.0
Cases	62		1739	4696

[a]Rates are per 100,000, age-adjusted to U.S. 1970 population. Source is New Mexico Tumor Registry of October 1976 for years 1969-1974. Rates are based on ICDA 8 classification but may be compared to rates based on ICD 6.