Leukemia Deaths in Minnesota 1950–64

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THE POSSIBILITY that leukemia may have a viral etiology has led many investigators to analyze the pattern of occurrence of the disease within communities. Recently there has been increasing speculation that leukemia may occur in clusters. Although more cases of leukemia occur in the older age groups than in the younger, exploration of the possibility of clustering has centered principally on the study of childhood leukemia because it offers greater ease of etiologic investigation.

Major impetus was given to the possibility that leukemia occurs in clusters by a report (*1*) of eight cases of leukemia in children who lived in the same neighborhood. Seven of the eight either attended, or had siblings who attended, the same school. An associated rheumatic type of illness occurred in pupils in the school along with a communitywide increase in deaths from congenital heart disease. Among other studies of the temporal-spatial distribution of leukemia, some have demonstrated case aggregation (*2–5*), and others have indicated a random distribution of the disease (*6–8*).

In 1949–51, there was a belt of high leukemia death rates across the northern part of the United States (*9*). By 1960, this belt had shifted to the general course of the Mississippi River (*10*). This belt was probably not the result of urbanization or of a high physician-population ratio. Some of the highest leukemia death rates in this belt were found in Minnesota, which consistently has had one of the highest death rates for leukemia of any State (*9–11*).

We undertook our study to analyze the trends of leukemia deaths in Minnesota. Consideration was given to the fluctuation in annual statewide death rates and to variations in death rates for individual counties during intervals within the period 1950–64. We found no significant increase in the annual statewide leukemia death rate during the period, and no area of the State had a persistently elevated leukemia death rate.

Methods

Estimation of the Minnesota population for intercensal years by county and age group was necessary before we could calculate age-adjusted leukemia death rates. Although the age structure of county populations was known for the census years 1950 and 1960 and independent estimates of total county population were available for each year of the period 1950–64, we could only estimate the actual yearly fluctuation of the age distribution.

Leukemia death rates were analyzed according to four age groups—persons under 15 years, 15–44 years, 45–64 years, and 65 years and over. To obtain estimates of each county's population according to these age groups, we calculated

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the percentage of the county population in each age group during 1950 and 1960. Then a hypothetical relationship between the national age structure and the county age structure was established by the ratio of the percentage in each age group in the county to the percentage in that age group in the United States. Ratios for the intercensal years were obtained by linear interpolation between the 1950 and 1960 county-national ratios for each county and each age group. We then calculated the actual size of the population groups for each county on the basis of the hypothetical relationship between the county and the national age structure and of the national figures available from the Bureau of the Census for each year. Rather than project the ratio of county to national percentage linearly beyond 1960, we decided to hold the 1960 ratio constant for the period 1960–64.

Death certificates were the ultimate source of information for our study. After the information had been placed on punchcards, we sorted these cards to obtain the necessary data. All death certificates which listed leukemia or aleukemia as the underlying cause of death during the years 1950–64 were analyzed. Deaths were attributed to the county of residence, not the county in which the patient died. The types of leukemia death rates analyzed were the crude rate—which was used to obtain a rough indication of rate uniformity by area and period, the age-specific rates, and finally, the age-adjusted rates.

The necessity for adjustment of rates by sex and 5-year age groups was evaluated. The age-sex specific rates for the entire State for 1960 by 5-year age groups were applied to six counties with different geographic locations and age structures. These rates were compared with the rates determined only on the basis of the four age groups (under 15 years, 15–44, 45–64, and 65 and over) with no adjustment for sex. If a rate adjusted for sex and age by 5-year age groups was the "ideal" rate, then age adjustment by the four age groups accounted for 97.2 percent of the difference between the crude and "ideal" rates. We then analyzed the county rates, using the four age groups without sex adjustment.

The nonwhite population of Minnesota in 1960 was 42,261, or 1.3 percent of the State population. American Indians made up approximately one-third of this nonwhite population. Because of the very small nonwhite population, we based all further calculations on the entire population, making no adjustments for race.

Leukemia death rates during the 15-year period were analyzed for the entire State and for each of the 87 counties. To obtain county rates that would be suitable for comparison when intervals within the 15-year period were analyzed, we combined some of the counties so that at least 80 percent of the counties had a population of 21,000 or more. This procedure resulted in our treating the data in 70 units—47 single-county units and 20 two-county units. The cities of Minneapolis, St. Paul, and Duluth were treated as separate units.

Calculation of the expected number of leukemia deaths in each county was based on the statewide age-specific leukemia death rate and on population estimates by age group for each county unit. The chi-square test was performed to determine whether the actual number of deaths during each interval was consistent with the expected number for all county units. In addition, the t-test with confidence limits of 95 percent was used to determine the county units in which the death rates differed significantly from statewide rates.

Results

The population of Minnesota, of each of its 87 counties, and of the cities of Minneapolis, St. Paul, and Duluth was calculated for every year from 1950 through 1964. In 1950, the county populations varied in size from 2,900 (Cook) to 676,579 (Hennepin). In 1964, Cook remained the smallest county (3,423) and Hennepin the largest (870,313). The age group with the most persons was the one 15–44 years old. The most striking gains in population were in the age group under 15 years (fig. 1).

Leukemia deaths. During the period 1950–64, there were 4,190 deaths due to leukemia in Minnesota. Approximately 60 percent of these deaths occurred in males (table 1). There were 668 leukemia deaths in children under 15 years—16 percent of the total deaths from leukemia, and there were 1,942 leukemia deaths in patients over 65 years of age—46 percent of the total leukemia deaths. The under-15-year age group

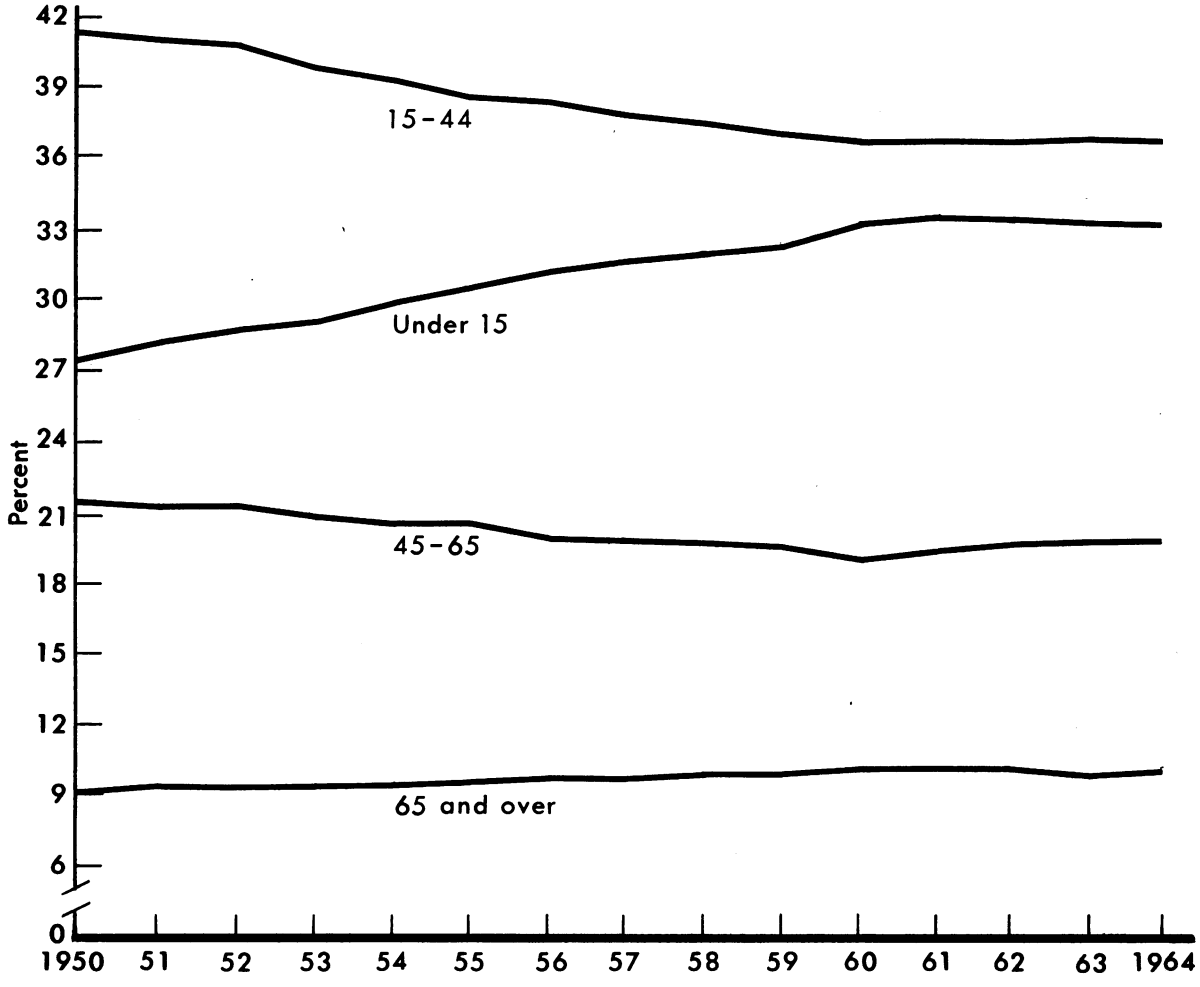
consistently accounted for approximately 16 percent of the leukemia deaths during the 15-year period.

The most common cell type of leukemia during the early 1950's was lymphatic (table 2). Although the number of deaths from both lymphatic and myelogenous leukemia increased during the 15-year period, acute unspecified leukemia accounted for the most deaths during the late 1950's and early 1960's. The predominance of this diagnosis may represent a true shift in cell type but is probably largely related to the 1955 revision of the International Classification of Diseases.

Statewide rates. The age-adjusted death rates for leukemia in Minnesota ranged from a high of 9.82 per 100,000 population in 1957 to a low of 8.11 per 100,000 in 1955 (table 3). The overall 15-year age-adjusted rate was 8.71 per 100,000. Although the annual age-adjusted rates fluctuate somewhat, there was no significant difference among these rates or among the 3-year rates. Although the leukemia death rate for males was consistently higher than the female rate, neither showed an indication of change (fig. 2). As expected, the highest age-specific death rates were found in the group over 65 years of age (fig. 3). The age-specific death rate for leukemia in children showed a significant downward trend during the 15-year period (linear trend equation: $\overline{Y}=4.410-.0875x$; $X_{1957}=0$), and the rates for persons over 65 years of age showed a significant increase (linear trend equation: $\overline{Y}=39.436+0.896x$; $X_{1957}=0$).

When the age group under 15 years was di-

Figure 1. Population of Minnesota by age groups, 1950–64



vided by sex, the change appeared to be due primarily to a significant decrease (P less than 0.05) in the rate for males under 4 years of age (fig. 4). The rates for females 0–4 years remained rather constant during the period 1950–62, while the male rate actually became less than that for females.

The age-specific leukemia death rates for males over 65 years of age were consistently almost twice as high as the corresponding female rates (fig. 5).

County variation in death rates. Age-adjusted annual death rates for leukemia for the entire State did not differ significantly over the years 1950–64. In some of the county units, however, the average rates for the 15-year period varied significantly from the average State rate for the period.

The statewide average annual age-adjusted death rate for leukemia for the 15-year period was 8.71 with a standard deviation of 0.13. The highest rate (14.27 per 100,000 population) was observed in Wabasha County, which is in southeastern Minnesota, along the Mississippi River.

Table 1. Annual leukemia deaths by sex and age group, Minnesota, 1950–64

Year	Total	Number in males					Number in females					Male to female ratio
		Under 15	15–44	45–64	65 and over	Total	Under 15	15–44	45–64	65 and over	Total	
1950	237	24	25	46	54	149	14	13	34	27	88	1.69
1951	258	27	17	50	57	151	22	19	30	36	107	1.41
1952	241	17	18	47	63	145	15	15	30	36	96	1.51
1953	253	28	17	36	71	152	18	13	27	43	101	1.50
1954	255	28	17	38	64	147	22	17	27	42	108	1.36
1955	255	22	13	37	76	148	13	24	26	41	107	1.38
1956	286	23	17	44	70	154	26	19	31	56	132	1.17
1957	319	26	23	41	87	177	27	14	33	68	142	1.25
1958	294	21	28	48	77	174	23	14	34	49	120	1.45
1959	293	35	19	42	89	185	12	17	32	47	108	1.71
1960	291	28	25	48	78	179	20	15	21	56	112	1.60
1961	295	24	16	43	99	182	23	6	28	56	113	1.61
1962	320	24	25	47	111	207	18	10	21	64	113	1.83
1963	286	23	23	24	90	160	29	14	30	53	126	1.27
1964	307	20	14	32	109	175	16	13	32	72	132	1.33
Total	4,190	370	297	623	1,195	2,485	298	223	436	746	1,705	1.46
Percent [1]	-----	14.9	11.9	25.1	48.0	100	17.5	13.1	25.6	43.8	100	------

[1] Based on total deaths in sex group.

Table 2. Annual deaths from leukemia by diagnostic classification, Minnesota, 1950–64

Year	Lymphatic	Myelogenous	Monocytic	Acute unspecified	Other unspecified	Total
1950	117	79	5	12	24	237
1951	122	77	12	19	28	258
1952	103	92	8	17	21	241
1953	120	94	3	11	25	253
1954	124	84	14	14	19	255
1955	99	85	16	24	31	255
1956	137	101	8	21	19	286
1957	153	102	13	24	27	319
1958	80	71	11	107	25	294
1959	86	69	8	102	28	293
1960	97	66	11	96	21	291
1961	94	77	17	88	19	295
1962	106	57	15	121	21	320
1963	66	66	16	109	29	286
1964	100	67	14	108	18	307
Total	1,604	1,187	171	873	355	4,190

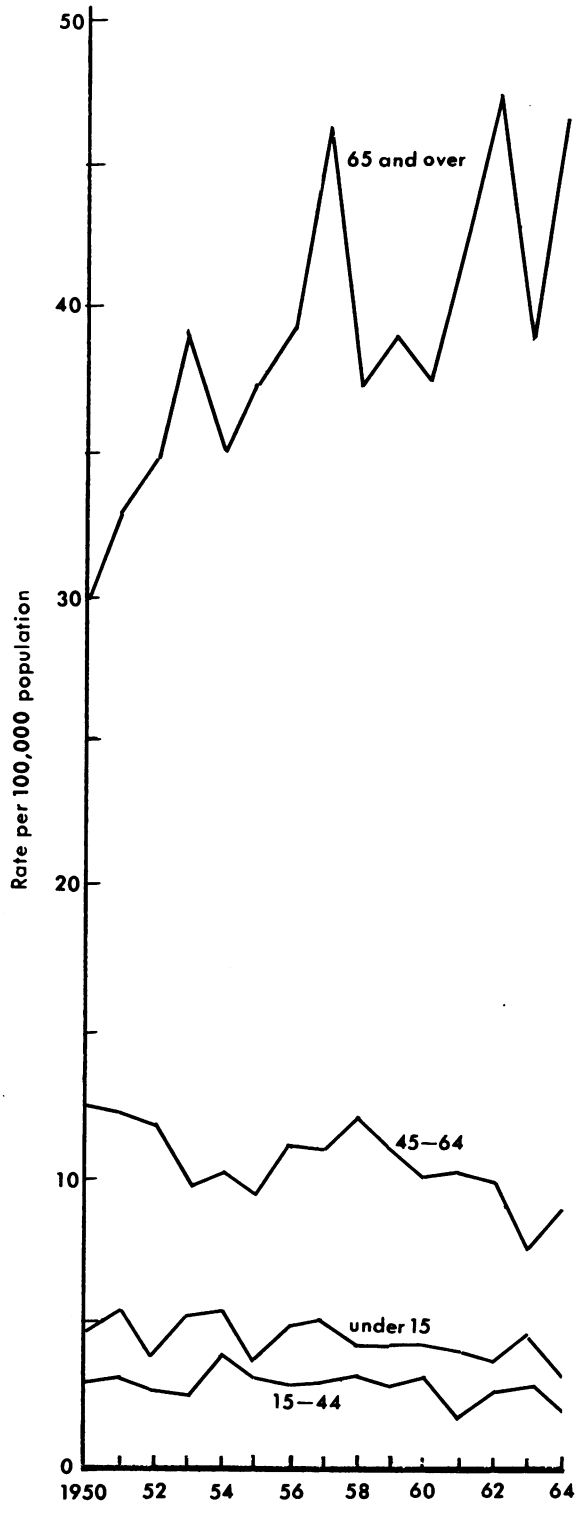
The lowest rate occurred in Lake of the Woods County on the Canadian border. The distribution of these average annual age-adjusted death rates did not indicate that any portion of the State had an elevated leukemia death rate (fig. 6). The distribution of rates, however, was not homogeneous (P less than 0.05). Five of the 87 counties and the city of St. Paul (table 4) had age-adjusted leukemia death rates for the 15-year period which varied significantly from the statewide rate (P less than 0.05), whereas only 4.4 units would have been expected to show such deviation. Nevertheless, the death rates for the city-county units did not form any geographic pattern.

We analyzed the leukemia death rates for each county unit in five 3-year intervals during 1950–64. When the homogeneity of the rate distributions for each of the 3-year periods was evaluated by chi-square, the 1956–58 interval was found to be nonhomogeneous (P=0.05). During that interval, four counties had age-adjusted leukemia death rates significantly higher than the statewide rates, while no county had a rate significantly below the statewide rates (table 5).

We undertook analysis of age-specific leukemia death rates for two groups, persons under 15 years—because leukemia is the leading cause of cancer deaths among children—and persons 65 years and over—because this age group accounts for the greatest number of leukemia

Figure 2. Age-adjusted leukemia death rates for males, females, and both sexes, Minnesota, 1950–64

Figure 3. Age-specific leukemia death rates for all age groups, Minnesota, 1950–64



deaths. To facilitate comparison of age-specific death rates for various areas, we divided the State into nine parts for the under-15 age group and into 16 parts for the age group 65 and over. These divisions were based on grouping the areas of the State having similar economic and social characteristics as delineated by the U.S. Bureau of the Census (*12*).

Application of the chi-square test to the data for the under-15 age group for the five 3-year intervals and for the 15-year interval revealed that the distribution of rates for the nine areas was homogeneous for each period. One area consisting of 15 contiguous counties to the north and west of the Twin Cities of Minneapolis and St. Paul (fig. 6) had an average age-specific leukemia death rate for the 15-year period significantly lower (P less than 0.05) than the State. As the following table shows, rates for this area were consistently below the corresponding State rates.

Years	*15-county rate*	*State rate*
1950–52	3.760	4.745
1953–55	2.599	4.650
1956–58	4.283	4.675
1959–61	1.994	4.160
1962–64	1.634	3.714
1950–64	2.80	4.46

Table 3. Crude and age-adjusted leukemia death rates per 100,000, by the year and by 3-year intervals, Minnesota, 1950–64

Year	Crude rate	Age-adjusted rates [1]	
		Annual	3-year
1950	7.946	8.241	----------
1951	8.571	8.932	8.30
1952	7.954	8.215	----------
1953	8.295	8.652	----------
1954	8.191	8.435	8.48
1955	7.945	8.112	----------
1956	8.827	8.978	----------
1957	9.743	9.822	9.15
1958	8.874	8.935	----------
1959	8.705	8.738	----------
1960	8.524	8.524	8.68
1961	8.531	8.512	----------
1962	9.164	9.141	----------
1963	8.190	8.170	8.68
1964	8.619	8.662	----------

[1] Based on 1960 population. The 15-year rate was 8.71.

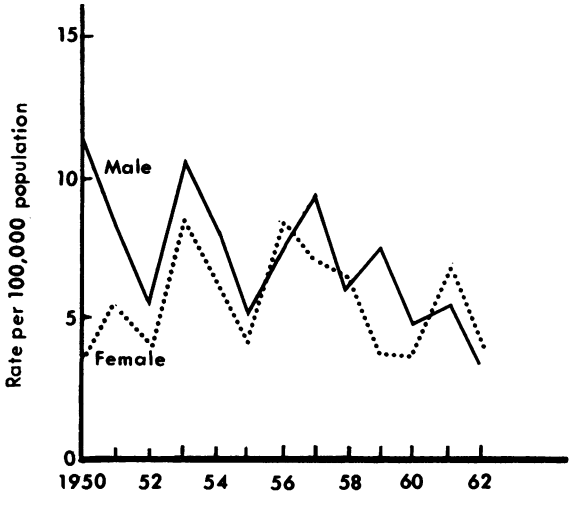
Analysis of age-specific leukemia death rates for the 65-and-over group yielded some narrow yet significant differences. During the 3-year period, 1962–64, the rates were not uniform among the 16 areas of the State. During that period, only the Rock County area rate (77.35 per 100,000 population) differed significantly from the corresponding statewide rate (46.24 per 100,000).

Analysis of the 15-year rates for the same age group also indicated nonuniformity (P less than 0.05). Again the Rock County area, and in addition St. Paul, had age-specific leukemia death rates which were significantly higher than the statewide rate.

Discussion

The primary purpose of our study was to examine the pattern of leukemia deaths in Minnesota in time and space. Nationwide leukemia death rates have shown a continuous increase for many years (*13*). This increase has generally been found in all age groups, in both sexes, and in the white and nonwhite. In contrast, our study did not show any significant increase in age-adjusted leukemia death rates for Minnesota during the period 1950–64. A previous study (*11*) indicated that the rate of increase in leukemia death rates was greatest in

Figure 4. Age-specific leukemia death rates for children 0–4 years by sex, Minnesota, 1950–62



SOURCE: Unpublished data of the Minnesota Department of Health.

Figure 5. Age-specific leukemia death rates for persons 65 years of age and over by sex, Minnesota, 1950–64

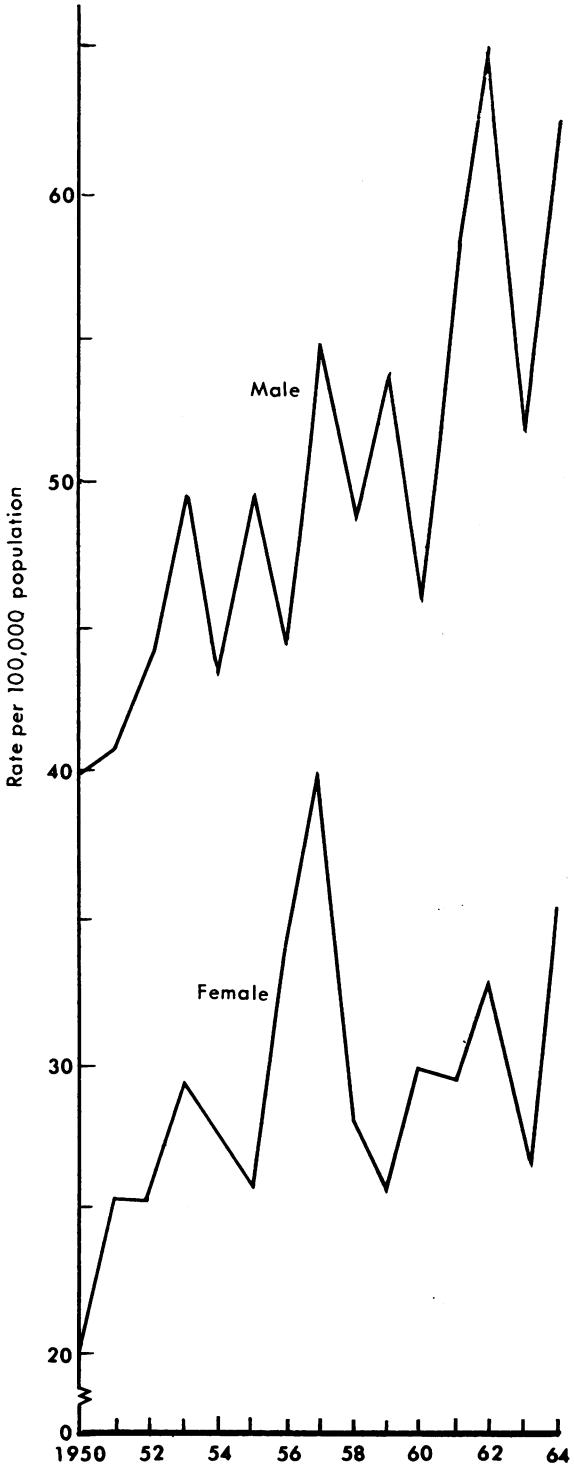
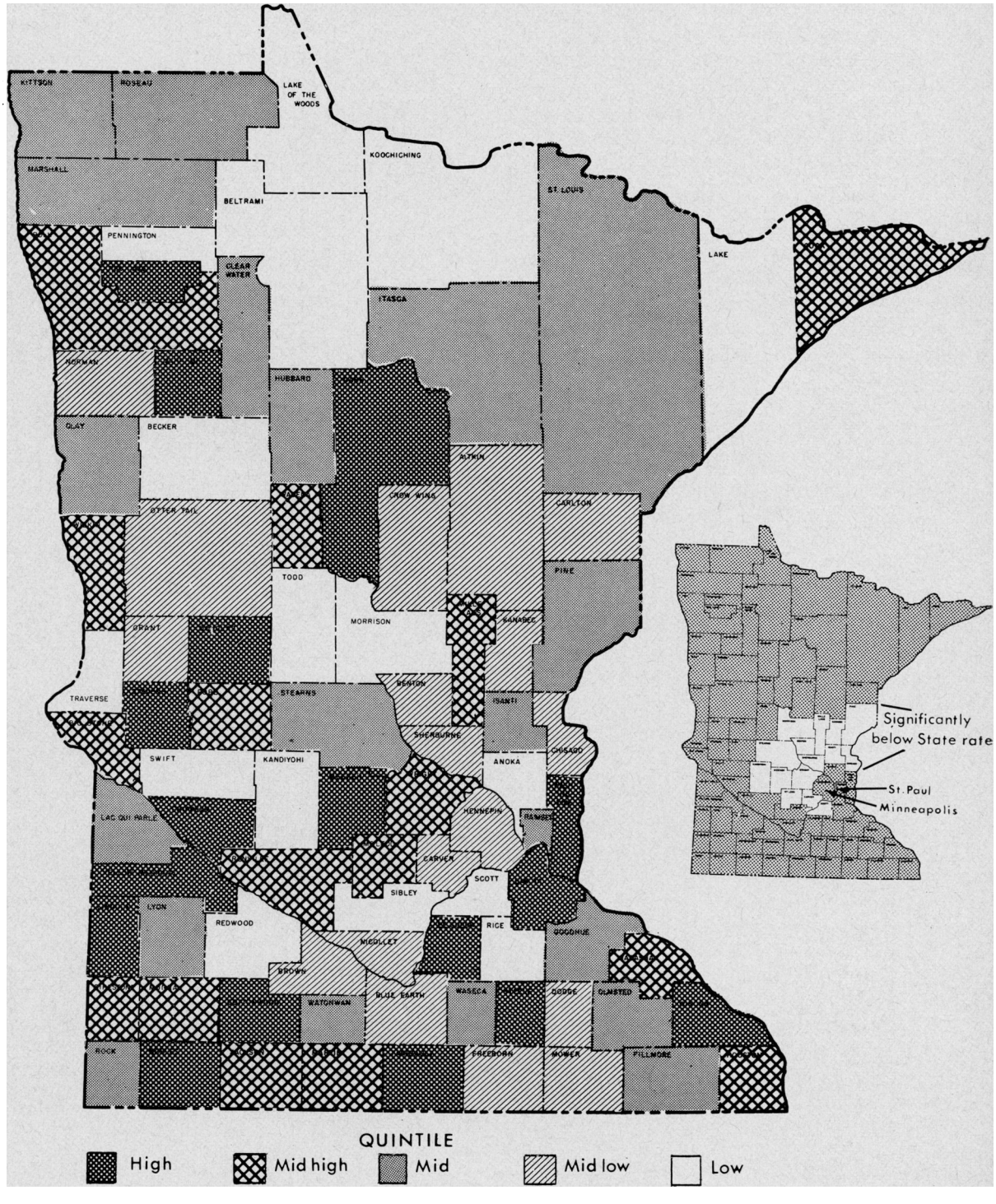


Figure 6. Age-adjusted leukemia death rates for Minnesota counties with inset showing 15-county area with rates for children under 15 years significantly below statewide rate, 1950–64



areas of the United States which previously had had the lowest death rates from the disease. Our study suggests that death rates in areas of high incidence may have reached their peak, and this possibility is reflected in the stability of national leukemia death rates (*14–17*).

Although the increase in leukemia death rates has occurred in all age groups, it has not been uniform. In about 1940, the increase in leukemia death rates began to slow down (*13*). This deceleration was most noticeable for the youngest age groups, becoming less marked with age, so that persons over 75 years showed no decline in the rate of increase. In our study, the only age group which showed a significant increase in leukemia death rates was the age group 65 and over. The age groups 15–44 and 45–64 years showed no evidence of either an increase or decline in death rates. There was a statistically significant decline, however, in the leukemia death rates for Minnesota children under 15 years of age.

Other studies have shown a decline in leukemia mortality beginning in the early 1940's for infants under 1 year of age (*13*, *15*, *16*). At approximately the same time, leukemia mortality for children 1 and 2 years of age began to remain constant (*15*). A decline in leukemia mortality began in about 1945 for 1-year-olds and in 1950 for 2-year-olds (*15*). Since 1955, the low rates for children less than 1 year old have shown no evidence of further decline.

The major factor in the decline of mortality for children under 15 years in Minnesota was the decline in death rates for males 0–4 years (fig. 4). Although we did not analyze the experience of children aged 0–4 years by single-year groups, this decline in death rates for the 0–4 year group seems in agreement with previous studies. It is unclear, however, why there should be a more marked decline in males 0–4 years than in females. Hernandez and Tokuhata (*18*) have shown that the leukemia death rate for children in Memphis and Shelby County, Tenn., has stabilized in recent years, but that boys have

Table 4. Units of Minnesota with average age-adjusted leukemia death rates for 1950–64 significantly different from average statewide age-adjusted rate

Unit	Number of deaths expected	Number of deaths observed	Age-adjusted death rate
Minnesota	4, 190	4, 190	8. 707
Anoka County	65. 8	47	5. 249
Kandiyohi County	41. 5	26	5. 415
Morrison County	33. 9	23	5. 916
Renville County	31. 7	45	12. 273
Wabasha County	24. 8	40	14. 270
St. Paul (city)	421. 9	495	10. 200

Table 5. Units of Minnesota with age-adjusted leukemia death rates for 3-year intervals significantly different from statewide rates for same intervals, 1950–64

Unit and period	Observed number of deaths	Expected number of deaths	Age-adjusted rate per 100,000
1950–52			
All Minnesota	736	736. 0	8. 30
Freeborn County	15	8. 4	15. 29
St. Louis County (except Duluth)	36	27. 2	11. 59
Beltrami County	1	5. 9	1. 52
Brown County	1	6. 7	1. 22
Lyon County	1	5. 4	1. 54
1953–55			
All Minnesota	760	760. 0	8. 48
Anoka County	3	10. 0	2. 95
Cottonwood and Jackson Counties	2	8. 1	2. 11
Ramsey County (except St. Paul)	5	12. 5	2. 55
1956–58			
All Minnesota	899	899. 0	8. 60
Big Stone County	7	2. 6	23. 25
St. Paul (city)	119	84. 9	12. 10
Wabasha County	12	5. 2	20. 75
Wright County	16	8. 5	16. 72
1959–61			
All Minnesota	879	879. 0	8. 68
Lyon County	12	6. 2	16. 66
Renville County	12	6. 6	15. 70
Wadena and Todd Counties	18	9. 9	15. 07
Anoka County	9	15. 7	4. 33
1962–64			
All Minnesota	912	912. 0	8. 68
Murray and Pipestone Counties	14	7. 3	16. 72
Renville County	13	6. 3	17. 55
St. Paul (city)	115	89. 0	11. 21
Anoka County	9	19. 9	3. 40

Table 6. Age-adjusted leukemia death rates for metropolitan areas of Minnesota for 15-year period and 3-year intervals, 1950–64

Unit	15-year rate	3-year rates				
		1950–52	1953–55	1956–58	1959–61	1962–64
Minneapolis	8.95	8.59	8.97	9.27	8.71	8.91
Hennepin County (except Minneapolis)	7.98	9.82	7.07	8.31	4.52	7.23
St. Paul	10.20	8.78	9.43	12.10	9.46	11.21
Ramsey County (except St. Paul)	8.61	6.91	2.59	6.96	10.96	9.42
Duluth	8.88	11.16	9.59	10.32	6.93	6.65
St. Louis County (except Duluth)	8.90	11.59	9.83	7.41	8.13	8.35

continued to have a greater risk of developing leukemia than girls.

Although overall Minnesota's leukemia death rates did not change during the 15-year period, increases in the rates for the older age groups were factors in forcing the statewide leukemia death rates upward. These upward forces were counterbalanced, however, by downward trends for the age group under 15 years. The leukemia death rates for the two age groups in the middle did not change significantly.

It appears likely that leukemia death rates are beginning to remain constant, most noticeably in States which have had the highest leukemia death rates in the past. The major factor in this constancy is a decline in leukemia death rates in the younger age groups. However, these declining rates have not yet clarified the etiologic role of prenatal drugs, viral or bacterial infections, prenatal irradiation, or genetic influences in childhood leukemia.

Analysis of the mean annual death rate for leukemia by county for the entire 15-year period showed that six county units had rates which differed significantly from the statewide rate. Although the leukemia death rates for these six do not form any recognizable geographic pattern, there is a suggestion that the rates may be higher in the southern half of Minnesota than in the more sparsely populated northern parts of the State (fig. 6).

Analysis of leukemia death rates for the county units by 3-year periods showed a nonhomogeneous distribution only during the 1956–58 period. Four county units showed statistically significant deviation from the State rate during that period—Big Stone on the western border of the State, Wabasha on the eastern border, St. Paul in the east central portion of the State, and Wright, northwest of St. Paul. Although the four units were all located in the southern half of Minnesota, their rates did not form any apparent geographic pattern.

In 1957, the statewide age-adjusted leukemia death rates for both sexes combined and for females separately were the highest found during the entire 15-year period. In that year, age-specific leukemia death rates for the age groups under 15 years and 65 years and over were among the highest encountered. The additional deaths in 1957 in the two age groups appeared to be due primarily to lymphatic leukemia in females. We do not know of any unusual factors, either statewide or in these four counties, which might have been operating during the preceding years or during 1957 as precipitating causes of death.

Three single-county units persistently had unusual age-adjusted leukemia death rates. Renville County had approximately twice as many leukemia deaths as expected during 1959–61 (6.6 expected, 12 observed) and again in 1962–64 (6.3 expected, 13 observed). Anoka County tended to have fewer deaths than expected. There was a significant difference between expected and observed deaths in Anoka for the entire 15-year period and for three of the five 3-year periods (1953–55, 1959–61, and 1962–64). This county, with a rather young population group, represents one of the major expanding suburban areas of the Twin Cities.

Most interesting of all our results, however, was the observation that the leukemia death rates for St. Paul were significantly elevated during two of the five 3-year intervals, while the rates for Minneapolis never differed significantly from the State norm. The mean annual leukemia death rate for Minneapolis dur-

ing the 15-year period was 8.95 per 100,000 population, a rate which differed significantly (P less than 0.05) from St. Paul's rate of 10.20 per 100,000. Throughout the 15-year period, St. Paul had a consistently higher leukemia death rate than Minneapolis (table 6). Minneapolis also had higher death rates than rural Hennepin County, and St. Paul had higher rates than Ramsey County. Duluth, however, did not have higher rates compared with St. Louis County.

As a result of our demonstration of the difference in leukemia death rates in St. Paul, a leukemia surveillance project has been initiated which will include prospective analysis of the patterns of occurrence of the disease in the metropolitan Twin City area.

Summary

Using death-certificate information, we analyzed the distribution of leukemia deaths throughout Minnesota during the period 1950–64. During these 15 years, the leukemia death rates for the total population showed no significant increase. Death rates for persons 65 years of age and over, however, increased significantly. A significant decrease in leukemia death rates in children under 15 years of age also occurred, caused primarily by a decreasing death rate in boys 0–4 years of age.

Our study supports previous suggestions that leukemia death rates are becoming constant in areas which have had high leukemia death rates in the past and that they are actually declining in some younger age groups.

No portion of the State had persistently elevated leukemia death rates, although they appeared to be higher in the more populous southern portion. The rates in St. Paul were consistently and significantly higher than in Minneapolis, and both cities had rates higher than the rural portions of the counties in which they are located.

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