Space-Time Clustering of Childhood Leukemia in San Francisco

Melville R. Klauber and Piero Mustacchi

University of Utah College of Medicine, Salt Lake City, Utah 84112, and University of California School of Medicine, San Francisco, California 94122

SUMMARY

Mantel's regression approach was used to test for space-time clustering for time of diagnosis and address of 149 leukemia cases in children under the age of 15 years diagnosed in San Francisco during the 20-year period 1946 to 1965. The cases were partitioned into consecutive time intervals, and the sum of the distances between pairs of cases falling within intervals was compared to its expectation, assuming a random allocation of space points to time points. Five different interval sizes were used: 0.5, 1, 2, 4, and 12 months. The 2-month intervals were chosen in advance for significance testing purposes at the 5% level. Separate analyses were performed for ages 0 to 14 and 2 to 14 years. Neither of the age groupings showed statistically significant clustering for 2-month intervals. The only analysis of this same type yielding a p value less than 0.05 was for ages 2 to 14 years and with 12-month intervals (p = 0.024).

A comparison of "within" time interval average distance between cases to "between" time interval average distance indicated that "clustering" in the series was weak. In addition, Knox's approach was used for descriptive purposes. The clustering appeared to be the result of a slight excess of pairs within relatively large time and/or large space distances.

Data are presented indicating that a single analysis of a case series with a long time span can be subject to artificial space-time clustering occurring in the population at risk.

INTRODUCTION

Since the report of an apparent cluster of childhood leukemia by Heath and Hasterlik (3) in 1963, a number of objective statistical methods have been proposed and applied to try to determine whether or not there is significant space-time clustering of this disease. Knox (5) used a 2 x 2 contingency table approach for the set of all spatial and temporal distances (by residence and time of onset) for leukemia cases with onset before age 6 in Northumberland and Durham (1951 to 1960). A significant excess of cases less than 1 km apart in residence and less than 60 days apart in time of onset was found. The same method was applied to data for leukemia cases with onset under age 15 years for Portland, Ore., and its environs. A significant excess was not found for cases less than 1 km and 60 days apart, but interaction was best shown for distances less than 4 km and 250 days apart (7). Barton et al. (2) applied the Barton-David approach (1) to Knox's data for Northumberland and Durham but found no significant space-time clustering.

For San Francisco, Mustacchi (8) found a form of spatial clustering for a case series which partially overlaps the series presented in this communication. A deficit of leukemia cases for all ages in the period 1949 to 1955 was discovered in those San Francisco census tracts where there had been an absence of leukemia cases for the period 1946 to 1948.

MATERIALS AND METHODS

San Francisco resident cases of leukemia in children under age 15 years diagnosed during the 20-year period January 8, 1946 to January 7, 1966, were identified through cooperation of the San Francisco Department of Public Health; San Francisco Medical Society; Stanford University Medical School; and administrative, medical, and record room staffs of every San Francisco hospital. Clinical charts and death certificates were searched for the diagnosis of leukemia.

Mantel's approach (6) was used in the present study. Two distance measures were computed, X a spatial measure and Y a temporal measure, for each of the n(n-1)/2 unordered pairs of cases. Let i and j index any pair of distinct cases. Statistically significant space-time clustering is evidenced by a large departure (in the appropriate direction) of the statistic

\[ W = 0.5 \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} X_{ij}Y_{ij} \]

from its expectation based on the assumption of random matching of the space and time coordinates. The spatial measure chosen was the distance in feet between the cases which was plotted to the nearest 100 feet. The temporal measure was defined as \( Y_{ij} = 1 \) if Cases i and j were diagnosed within the same time interval and \( Y_{ij} = 0 \) otherwise.

W is merely the sum of spatial distances between all pairs of cases that were both diagnosed within the same time interval.

Five different time intervals were investigated: 0.5, 1, 2, 4, and 12 months. The 2-month interval was the predetermined value chosen for significance testing purposes at the 5% level. Each of the 5 sizes of intervals consisted of 1 or more consecutive 0.5-month intervals: January 8 to January 22, January 23 to February 7, February 8 to February 22, etc. This unusual arrangement of intervals was chosen in order to make the intervals approximately the same length and at the same time to try to reduce the likelihood of misclassification. Each study year, starting at January 8, was divided into 24 0.5-month intervals, 7 of 16 days, 16 of 15 days, and 1 of 13 days (14 days in leap years). In the case series, the day of the month was 1 for 37% of the cases and 15 for 32% of the cases. By

1 This investigation was supported by USPHS Grants CA 05924 and 9751 and the Laurence and Alice Anspacher Myers Fund.

Received May 20, 1968; accepted March 20, 1970.
"centering" the 0.5-month intervals on the 1st and 15th days of the month, it was hoped to reduce misclassification errors that might arise if the division had been made closer to the 1st and 15th days of the month.

Approximate p values were determined by treating the standardized statistic \( (W - \text{Exp} \ W) / \sqrt{\text{Var} \ W} \) as a normally distributed random variable. The reader is referred to Ref. 6 for the formulas used to compute Exp \ W and Var \ W and for extensive discussion of the method and its relationship to a number of other approaches to the space-time clustering problem.

It was necessary to reduce space-time clustering due to varying population growth rates in different neighborhoods during the 20-year period. The 1950 and 1960 census data for San Francisco persons ages 0 to 14 years indicated that the rate of population growth varied considerably from census tract to census tract; 35% of the tracts had 25% or more deviation from expected population in 1960 based on the assumption that each tract had the same growth rate during the previous 10 years for ages 0 to 14 years as the whole city (9). In order to reduce the effect of this artifactual clustering in the population at risk, the case series was analyzed in 4 separate 5-year periods: January 8, 1946 to January 7, 1951; January 8, 1951 to January 7, 1956, etc. Summary (normal) p values were obtained with the statistic

\[
(\Sigma W - \Sigma \text{Exp} W) / \sqrt{\Sigma \text{Var} W}
\]

The data were analyzed separately for the full 15-year age group and ages 2 through 14 years. It was thought that clustering might be enhanced by eliminating the children diagnosed during the first 2 years of life, since these children may have acquired the disease as a result of a congenital condition. A supplementary analysis with reciprocal spatial and temporal measures was performed to determine whether the use of time intervals and a distance measure which does not give extra weight to short distances obscured the degree of clustering.

Two further analyses are presented for descriptive rather than significance testing purposes. For each time interval size used in the Mantel approach, a comparison was made of "within" time interval average distance between cases to the "between" time interval average distance. Knox's approach (5) which compares the number of pairs of cases less than a given spatial distance and less than a given temporal distance to expectation was tried for the 16 combinations obtainable for the spatial distances 0.25, 0.5, 1, and 2 miles with the temporal distances 30, 60, 120, and 365 days. Knox's approach provides additional descriptive information over the average distance approach in that it shows the excess of pairs within

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>Pairs averageda</th>
<th>Distance (ft) at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 mo.</td>
<td>1 mo.</td>
</tr>
<tr>
<td>0–14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within intervals</td>
<td>18,630</td>
<td>17,080</td>
</tr>
<tr>
<td>Between intervals</td>
<td>(25)b</td>
<td>(55)</td>
</tr>
<tr>
<td>2–14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within intervals</td>
<td>19,420</td>
<td>17,360</td>
</tr>
<tr>
<td>Between intervals</td>
<td>(15)</td>
<td>(38)</td>
</tr>
<tr>
<td>(1,777)</td>
<td>(1,754)</td>
<td>(1,728)</td>
</tr>
</tbody>
</table>

a The spatial coordinates of the residences were determined to the nearest 100 feet, and the averaged distances were rounded to the nearest 10 feet. Pooled averages are given from the 4 separate 5-year analyses.

b No. of pairs shown in parentheses.
various distances in both dimensions. Knox’s approach was not used for statistical significance testing; however, Knox’s statistic has the form of a Mantel Z-statistic and may be tested by Mantel’s approach.

### RESULTS

For the predetermined time interval of 2 months for ages 0 to 14 years a nonsignificant \(p\) value of 0.32 was obtained; for ages 2 to 14 years the \(p\) value was reduced only slightly (0.26). Table 1 shows that there appears to be a trend of greater “within time intervals” average with larger time intervals, especially for the 2- to 14-year age groups. For 12-month intervals, the \(p\) values are 0.19 for ages 0 to 14 years and 0.024 for ages 2 to 14 years. Evidently, removing cases diagnosed during the first 2 years of life did enhance the space-time clustering considerably when 12-month intervals were used.

The average distance in feet between residences of the cases for those pairs within the same time intervals and those pairs not in the same time intervals were computed for each 5-year period, the 5 interval lengths, and the 2 age groupings. The 40 differences in averages were so small that only the pooled averages are shown in Table 2; the largest difference in averages among the 4 5-year periods was for 1956 to 1960 with 12-month intervals, where the “within time intervals” average was 15,740 feet and the “between time intervals” average was 17,710 feet. In Table 2, the pooled averages were obtained merely by summing the distances between the indicated pairs from the individual cases.

**Table 4**

<table>
<thead>
<tr>
<th>Year, mo./day</th>
<th>Coordinates (V = No. of 100 feet east of origin, W = No. of 100 feet north of origin), age in years, and sex</th>
<th>Year, mo./day</th>
<th>Coordinates</th>
<th>Year, mo./day</th>
<th>Coordinates</th>
<th>Year, mo./day</th>
<th>Coordinates</th>
<th>Year, mo./day</th>
<th>Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1946</td>
<td>1/1</td>
<td>69</td>
<td>133</td>
<td>2</td>
<td>M</td>
<td>6/1</td>
<td>57</td>
<td>252</td>
<td>10</td>
</tr>
<tr>
<td>1947</td>
<td>5/1</td>
<td>187</td>
<td>260</td>
<td>0</td>
<td>M</td>
<td>7/1</td>
<td>66</td>
<td>235</td>
<td>6</td>
</tr>
<tr>
<td>1948</td>
<td>7/1</td>
<td>48</td>
<td>328</td>
<td>5</td>
<td>M</td>
<td>8/1</td>
<td>193</td>
<td>305</td>
<td>4</td>
</tr>
<tr>
<td>1949</td>
<td>7/1</td>
<td>157</td>
<td>61</td>
<td>7</td>
<td>M</td>
<td>10/20</td>
<td>348</td>
<td>312</td>
<td>2</td>
</tr>
</tbody>
</table>

JULY 1970

1971

Downloaded from cancerres.aacrjournals.org on April 12, 2017. © 1970 American Association for Cancer Research.
5-year analyses and dividing by the number of pairs. In no case did the “within intervals” pooled average distance exceed the “between intervals” average by as much as 1,000 feet.

The observed and expected pairs less than various space and time distances apart are shown in Table 3. These indicate that the smaller “within” than “between” average distance for intervals of 1 month or longer in Table 2 were not due to excessive numbers of cases occurring very close to each other. It appears that there are slightly more than expected pairs less than 0.25 mile apart, close to the expected number less than 0.5 and 1 mile apart, and more than expected less than 2 miles apart. One of the largest observed to expected ratios obtained, 9/5.1 for the age group 2 to 14 years, for pairs less than 0.25 mile and 365 days apart, involved only 11 cases. One case was in 3 pairs, 5 cases were in 2 pairs, and the remaining 5 cases appeared in only 1 pair. The data in Table 3 are taken from the 11,026 pairs obtainable from the 149 cases ages 0 to 14 and the 7,260 pairs from the 121 cases ages 2 to 14 for the full 20-year period and hence may be affected by space-time clustering in the population at risk. For descriptive purposes, it was thought desirable to identify the extent of excess pairs of “close” cases for the whole period.

Table 4 provides a complete listing of cases in chronological order of diagnosis and shows the coordinates of the home address, sex, and age at time of diagnoses.

Further analysis of the present data clearly indicated the necessity of dividing the 20-year period in order to reduce the effect of space-time clustering of the population at risk. When the analysis was repeated with the whole 20-year series as a single unit, all 10 p values were reduced from what they were for the summary statistic from the four 5-year analyses. The largest absolute and proportional reductions were 0.19 to 0.13 (ages 0 to 14 years, 12-month intervals) and 0.024 to 0.015 (ages 2 to 14 years, 12-month intervals), respectively.

By using the time measure which identifies whether or not pairs of cases lie in the same time interval, the problem of errors in time measurements was mitigated, but this ran the risk of putting children whose address and time of diagnosis were close into separate intervals. For determination of whether or not the separation of cases into time intervals and the use of untransformed spatial distances did in fact obscure clustering, the analysis was repeated in the same way, except with different space and time measures. The reciprocal measure suggested by Mantel (5) was used for both measures:

\[ X_{ij} = 1/(K_s + D_{ij}) \]
\[ Y_{ij} = 1/(K_t + T_{ij}) \]

where \( K_s \) and \( K_t \) are constants and \( D_{ij} \) and \( T_{ij} \) are the distance in feet and time separation in days, respectively, between Cases \( i \) and \( j \). The 25 combinations of constants obtainable from the values \( K_s = 100, 500, 2,500, 12,500, 62,500 \) and \( K_t = 15, 30, 60, 120, 365 \) were tried for both age groups, 0 to 14 years and 2 to 14 years. The range of \( p \) values obtained for ages 0 to 14 years was 0.058 to 0.49 (\( p = 0.058 \) occurred with \( K_s = 62,500 \) and \( K_t = 60 \)); for ages 2 to 14 years, the range of \( p \) values was 0.020 to 0.49 with 7 of the 25 values less than 0.05 (\( p = 0.020 \) occurred with \( K_s = 62,500 \) and \( K_t = 120 \)). Apparently, no serious division of “clusters” occurred for the age group 2 to 14 years when the interval time measure was used. For ages 0 to 14 years, the minimum \( p \) value obtained with the reciprocal transformation was 0.058 compared to 0.17 with the interval distance measure; but with the former measure, 5 times as many forms of the test were tried as with the latter, and none of all 30 results were significant at the 5% level.

The 6 of the 7 “significant” \( p \) values were probably little affected by the time measurement errors mentioned above, since they involved the use of additive time constants, \( K_t \) of 60 (days) or more.

DISCUSSION

The problem of assessing the statistical significance of a number of space-time clustering studies of a rare disease is hard because the replication of studies under similar conditions is difficult, if not impossible. Because of differences in geography and population density, results obtained in 1 area cannot be definitively confirmed or refuted by a study in another area. If one wishes to repeat a study in the same area, since the disease is rare, a great deal of time is required and, with the passage of time, important changes in population density and distribution can occur. This makes it desirable to try a variety of space and time measures in order to elucidate the nature of the clustering, if there be any. When a number of measures are used for the same data, the probability values obtained become nominal. Further interpretation of them is clouded by the statistical dependence of one such result upon another. In the present study, the problem of interpreting the \( p \) values is academic, since even if the space-time clustering is real, it is weak.

The residence of the child in a relatively compact highly urbanized city, such as San Francisco, may not be an appropriate spatial location for studies of space-time clustering. A child in San Francisco may easily come into contact with large numbers of persons who live throughout the city, but a child living in a suburban or rural community is likely to be in contact with far fewer persons. Likewise, an environmental agent which may be present in a small area can potentially affect a much higher percentage of a dense population than of a less dense population of the same size.

Is this to say that investigation of space-time clustering of leukemia cases as a means of elucidating the etiology of the disease is bankrupt? No, what is needed is some continued use of the general approach, but with more meaningful observations. An unsuccessful attempt at this was a study of hospital of birth clustering by Klauber (4). Other attempts should be made with the use of observations of times and places consistent with a given hypothesis of a given type of leukemogenic exposure.
ACKNOWLEDGMENTS

We are grateful to Nathan Mantel of the National Cancer Institute for allowing us the use of a prepublication copy of Ref. 6 and for a number of suggestions that led to improvement in this communication, especially the suggestion to split the time period and to observe the effect of eliminating cases under the age of 2 years. However, we bear the responsibility for any errors. We are indebted to Richard Walster for computer programming and the University of Utah Computer Center for time on the UNIVAC 1180 computer.

REFERENCES

Space-Time Clustering of Childhood Leukemia in San Francisco

Melville R. Klauber and Piero Mustacchi


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/30/7/1969

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.