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CHILDHOOD CANCER CLUSTERS IN NEW MEXICO, 1973-1997

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Abstract. Childhood cancer has been a growing problem in the United States with approximately 8,000 new cases reported annually for children under the age of 15. The first step in epidemiological studies of childhood cancer is usually to identify places with elevated rates. Past research placed particular emphasis on childhood cancer in children living near nuclear facilities. This study tests whether statistically significant clusters of childhood cancer, leukemias, acute lymphoblastic leukemia, or brain cancer are present in New Mexico where a nuclear research station is located. In the analysis, cancer incidence rates were adjusted for race (white, black, and other), age group, and sex. The results show that a statistically significant cluster of childhood cancer exists in Los Alamos County and in the six counties west and southwest of Los Alamos County when all cancers are considered. In addition, a statistically significant cluster of acute lymphoblastic leukemia exists in the state with concentration in Bernalillo, Cibola, Valencia, Socorro, and Dona Ana counties. No cluster of brain cancer was detected, and no cluster was detected when all leukemia incident cases were examined. Future research will need to search for possible risk factors responsible for the formation of the clusters.

Keywords: *childhood cancer, cluster analysis, leukemia, nuclear facility, GIS.*

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Introduction

Childhood cancer is a growing problem in the United States with approximately 8,000 new cases reported annually for children under the age of 15 (Carroquino et al. 1998, Schmidt 1998, Ries *et al.* 1999). Another worrisome aspect of this problem is that childhood cancer rates have been trending up at an annual rate of 1% for all cancers and 5% for acute lymphocyte leukemia (Carroquino *et al.* 1998). The most common childhood cancers are brain cancer and leukemias, which account for more than half of all childhood cancer incident cases. A very interesting phenomenon related to childhood cancer is that incident cases tend to cluster in space and time, meaning that children living at some places at certain times have elevated cancer rates.

Cluster analysis of childhood cancer, particularly for children living near nuclear facilities, has received much attention for nearly two decades (Shlein, Ruttenber, and Sage 1991; Laurier and Bard, 1999; Little, 1999). Although some studies have identified clusters of cancer in populations living near nuclear facilities in places like Sellafield/Seascale, England (Black 1984), Dounreay, Scotland (Black and Sharp 1993), La Hague, France (Viel, Pobel, and Carre 1995), in Germany (Hoffman et al 1997), and in counties near Oak Ridge National Laboratory in Tennessee in the United States (Mangano 1994) results from most studies have been negative (Baron 1984; Alexander et al. 1990; McLaughlin et al. 1993; Bithell *et al.* 1994; Waller et al. 1995; Hjalmers et al. 1996; Kaatsch *et al.* 1998; and Jablon, Hrunes, and Boice 1991). So far, the most extensive and comprehensive cluster analyses of childhood cancer have been carried out in Europe, particularly in the United Kingdom. For example, Freda Alexander (1998) reported a clustering analysis of childhood leukemia in 17 European countries. In contrast, few cluster analyses of childhood cancer have been reported in the United States despite the fact that childhood cancer has been a growing problem. As a surveillance tool, regular cluster analysis in some selected areas could improve public health practice.

The author analyzed 1,083 individual incident (morbidity) cases of all cancers, 365 cases of leukemias, 294 cases of acute lymphoblastic leukemia, and 196 cases of brain cancer for children under the age of 15 in New Mexico using childhood cancer incidence data from 1973 to 1997. The results show that a statistically significant cluster of childhood cancer exists in Los Alamos County and in the six counties west and southwest of Los Alamos County when all childhood cancers are considered. In addition, a cluster of childhood acute lymphoblastic leukemia exists in the central-southwest part of the state with concentrations in Bernalillo, Cibola, Valencia, Socorro, and Dona Ana counties. No cluster of brain cancer was detected, and no cluster was detected when all leukemia cases were examined.

There are several reasons to choose the state of New Mexico for a cluster analysis of childhood cancer. First, there have been public concerns about the possibility of elevated incidence of cancer cases in Los Alamos and its neighboring counties (Kulldof *et al.* 1997). Because children are the most vulnerable, a cluster analysis would help answer questions from the public as to whether or not statistically significant clusters of childhood cancers

indeed exist in and near Los Alamos. Second, New Mexico is one of the states from which the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) collects cancer data. There are quality cancer incidence data and population data in New Mexico for a period of 25 years as of this writing. Third, most cluster analyses of childhood cancer reported in the literature were concerned with commercial power plants and nuclear waste processing plants. The nuclear research station at the Los Alamos National Laboratory is very different from those nuclear facilities in that radiation is largely from atmospheric weapons testing, not directly from the laboratory. Scientists and people living in New Mexico have had exposure to atmospheric weapons testing. Therefore, cluster analyses of childhood cancer in New Mexico may help gain more insights about the relationship between childhood cancer clusters and nuclear atmospheric testing research facilities.

Method and Data

The author employed the Spatial Scan Statistic method used by Kulldorff and his colleagues (Kulldorf *et al.* 1998) in this study. The Spatial Scan Statistic has been implemented in the SaTscan (Version 2.1.3) software package. This package is available from the United States National Cancer Institute (NCI). A detailed description of the Spatial Scan Statistic can be found in Kulldorff (1997). Only a brief description of the method is given in this discussion. The input data consists of three data sets: the case file, the at-risk population file, and the geographic location file. Once the data files are input to the software, the Spatial Scan Statistic first draws circles centered at county centroids in the study area based on coordinates given in the geographic location file. At each centroid, the sizes of the circles vary continuously based on a pre-specified maximum circle size (usually no larger than a circle containing 50% of the at-risk population in the study area). Counties whose centroids fall within a circle are considered covered by that circle. The method then computes the numbers of cases inside and outside each circle. Second, the method determines the cancer rates based on the case file and the population file, and then calculates the number of expected cases inside the circle based on the at-risk population in the counties whose centroids fall within the circle. The method adjusts the cancer rates using covariates given both in the case file and the at-risk population file.

Third, the method determines the most likely cluster and secondary clusters. A cluster usually contains one or more counties whose centroids fall within the circle under consideration. The method computes the likelihood ratio associated with each circle based on the values of the parameters obtained in previous steps. If a cluster has the maximum likelihood ratio and the number of observed cases within the cluster is more than its number of expected cases, then the cluster is the most likely cluster. Other clusters with smaller maximum likelihood ratios but with the number of observed cases exceeding its number of expected cases are considered secondary clusters. Clearly, secondary clusters are less important than the most likely cluster.

Fourth, the Spatial Scan Statistic method evaluates the statistical significance of the most likely cluster and secondary clusters using Monte Carlo simulations. Under the null

hypothesis, when cancer cases are assumed to follow the Poisson distribution in space, no statistically significant spatial clusters exist. This assumption implies that the simulated p value associated with the most likely cluster should be greater than 0.05 at the significance level of 0.05 and the maximum likelihood ratio should be less than a value determined by the method. Otherwise, the null hypothesis of no spatial cluster is rejected and the most likely cluster is a statistically significant cluster. The significance of secondary clusters is evaluated in a similar manner.

There are several reasons to choose the Spatial Scan Statistic for the analysis. First, the Spatial Scan Statistic method does not have the problem of multiple testing found in some exploratory analysis methods (Openshaw et al 1987, Fotheringham and Zhan 1996, and Rushton and Lolonis 1996). Similar to the Spatial Scan Statistic, these exploratory analysis methods draw circles centered at county centroids of the study area. But these exploratory analysis methods evaluate the significance of the cluster covered by each circle. This characteristic introduces the problem of multiple testing. In contrast, the Spatial Scan Statistic uses the maximum likelihood ratio to select the most likely cluster and secondary clusters, and it only evaluates the statistical significance of the most likely cluster and secondary clusters, not every cluster covered by each circle. The Spatial Scan Statistic thus avoids the problem of multiple testing (Kulldorf 1998). In addition, the Spatial Scan Statistic does not require a user to specify the size of a cluster before the clustering takes place, whereas this user input is required in the method developed by Turnbull and his colleagues (Kulldorf 1998, Turnaball et al. 1990).

The author prepared four case files containing cases of different cancers for children between the ages of 0 and 14 (inclusive) in all 33 counties in New Mexico over the 25-year period. Records of the individual cases were extracted from the Public-Use CD-ROM (1973-1997) provided by the Surveillance, Epidemiology, and End Results (SEER) Program of the NCI. Case File One contained 1,083 cases of all childhood cancers. Case File Two contained 365 cases of all childhood leukemias. Case File Three contained 294 cases of childhood acute lymphoblastic leukemia. Case File Four contained 196 cases of childhood brain cancer. For each case, county of residence of each case (county code) at the time of diagnosis, year of diagnosis of each case, and three covariates, race (white, black, and other), age group (five-year interval), and sex, were obtained.

A population file containing the annual at-risk population data for children between the ages of 0 and 14 (inclusive) in each county in New Mexico for each year over the 25-year period was prepared. The population data were obtained from the population database provided by the SEER program at NCI. To match the covariates in the case file, the population counts were cross-tabulated by race (white, black, and other), age group, and sex.

A location file containing the geographic coordinates of the centroid of each county polygon of all counties in New Mexico was prepared. It should be noted that New Mexico split one county into two counties (Cibola and Valencia) in 1982. Accordingly, for years 1982-97, cancer case data and population data in Cibola County were treated as those in Valencia County for convenience of analysis. Polygons representing these two counties were

merged in order to obtain the centroid of the merged polygon. The geographic coordinates of the centroid of the merged polygon were used to represent the location of the combined counties.

The author recognizes that it is more desirable to use a geographic area unit smaller than a county for the analyses reported in this study. But analyses using smaller geographic area units (e.g., census tracts) would require individual location data of cancer incident cases that were simply not available at the public domain. Another important reason to use county as the area unit for the analyses is that reliable yearly estimations of the *at-risk population* at the county level were readily available from the United States Bureau of the Census. Accurate at-risk population data are absolutely essential for obtaining reliable spatial clusters.

During the analyses, the size of the maximum circle was set to contain no more than 50% of the total at-risk population in the entire state. This size ensures that there is no pre-selection bias in the location and size of a cluster in the cluster analysis.

It should be pointed out that the analyses assumed that exposure over time for all factors other than population size, and age and race composition was equal for the study period spanning a quarter century. It is possible that potential exposures such as airborne, waterborne, transdermal, genetic mix, personal behaviors, and half-life of toxics could have changed at different locations throughout the state during the 25-year period. A more comprehensive study would need to include some, if not all, of these factors. Nevertheless, the goal of this study was to identify childhood cancer clusters in the state of New Mexico so that we can plan more focused studies targeting specific exposures in areas with detected clusters. Environmental exposure assessment related to these factors, however, remains a challenging issue in environmental science and spatial epidemiology.

Results

Analysis results of the four case files are reported in Table 1. For each detected cluster, counties/county in the cluster, the number of observed cases, the number of expected cases, the ratio between the number of observed cases and the number of expected cases, the log likelihood ratio, and the p-value are reported (Table 1). It should be noted that a detected cluster is not necessarily statistically significant. Statistically significant clusters were detected in Case File One (all childhood cancer cases combined) and Case File Three (childhood acute lymphoblastic leukemia cases). No statistically significant clusters were detected in childhood brain cancer cases and in all leukemia cases although the p-value associated with the most likely cluster of all leukemia cases is relatively low (p=0.0776).

(Table 1 about here)

The detected clusters related to all childhood cancer cases combined and childhood acute lymphoblastic leukemia cases are shown in Figure 1. In addition, the number of observed cases and the number of expected cases in each county in the most likely clusters are also shown (Figure 1). Because no statistically significant clusters exist in all leukemia cases

Table 1. Cluster Analysis Results of Childhood Cancer in New Mexico, 1973-97. (Note: Only detected clusters are reported in this table. Covariates used in the analysis were race, age group, and sex. Clusters with thire associated p-values underlined are statistically significant clusters at the significance level of 0.05.)

Cluster	County within a cluster	No. of observed cases	No. of expected cases	Observed to expected ratio	Log Likelihood ratio	p Value
All childhood cancers (Total no. of cases in the state: 1,083; No. of cases in clusters: 664)						
Most likely cluster	San Juan, McKinley, Cibola, Los Alamos, Sandoval, Bernalillo, Valencia	610	537.3	1.135	9.78	0.0010
Secondary cluster 1	Luna	21	13.56	1.548	1.77	0.8252
Secondary cluster 2	De Baca, Guadalupe, San Miguel	33	24.45	1.350	1.38	0.9305
All childhood leukemias (Total no. of cases in the state: 365; No. of cases in clusters: 168)						
Most likely cluster	Cibola, Sandoval, Bernalillo, Valencia	167	137.66	1.213	4.91	0.0776
Secondary cluster 1	Harding	1	0.22	4.452	0.72	0.9987
Childhood acute lymphoblastic leukemia (Total no. of cases in the state: 294; No. of cases in clusters: 166)						
Most likely cluster	Cibola, Bernalillo, Valencia, Torrance, Catron, Socorro, Lincoln, Sierra, Dona Ana	165	135.08	1.222	6.11	0.0214
Secondary cluster 1	Harding	1	0.18	5.510	0.89	0.9923
Childhood brain cancer (Total no. of cases in the state: 196; No. of cases in clusters: 80)						
Most likely cluster	Catron, Socorro, Sierra, Grant, Cibola, Valencia, McKinley	37	23.75	1.558	3.67	0.2184
Secondary cluster 1	Guadalupe, De Baca, San Miguel	11	4.54	2.438	3.43	0.2681
Secondary cluster 2	Los Alamos, Santa Fe, Sandoval, Rio Aribba	32	25.35	1.263	0.94	0.9868

combined (Case File Two) and in childhood brain cancer (Case File Four), the detected clusters related to these two case files are not shown. Among the three detected clusters in all childhood cancer cases combined, only the most likely cluster is a statistically significant cluster (p=0.0010). This cluster contains Los Alamos County and other six counties west and southwest of Los Alamos. These six counties are San Juan, McKinley, Cibola, Sandoval, Bernalillo, and Valencia. The two secondary clusters of all childhood cancers combined are not statistically significant at either the significance level 0.01 or 0.05 (Table 1 and Figure 1(a)).

(Figure 1 about here)

The number of observed cases (354) in Bernalillo County accounts for more than 58% of the 610 cases in the most likely cluster. This is to be expected because Bernalillo County has more than half of the population in the cluster. With the exception of San Juan, the number of observed cases in all other counties in the cluster exceeds the number of expected cases. Los Alamos County has the highest ratio between the number of observed cases and the number of expected cases (1.33), followed by Cibola/Valencia Counties (1.30), Mckinley (1.24), Sandoval (1.19), Bernalillo (1.11), and San Juan County (0.98).

Two clusters were detected in childhood acute lymphoblastic leukemia cases, but only the most likely cluster is statistically significant (p=0.0214). This most likely cluster contains nine counties including Cibola, Bernalillo, Valencia, Torrance, Catron, Socorro, Lincoln, Sierra, and Dona Ana counties. The secondary cluster of childhood acute lymphoblastic leukemia cases contains Harding County only and it is not statistically significant (Table 1 and Figure 1(b)). Again, the number of observed cases (107) in Bernalillo County accounts for nearly 65% of the 165 cases of childhood acute lymphoblastic leukemia in the most likely cluster. Counties with the number of observed cases exceeding the number of expected cases in the cluster include Cibola, Bernalillo, Valencia, Socorro, and Dona Ana counties. Clearly, these five counties are the counties contributing to the formation of this cluster of childhood acute lymphoblastic leukemia. The ratios between the number of observed cases and the number of expected cases in these five counties are: Socorro County (1.41), Dona Ana County (1.27), Bernalillo County (1.24), and Cibola/Velancia (1.21).

Discussion

This study has uncovered two statistically significant childhood cancer clusters in the state of New Mexico. This first cluster is related to all childhood cancers and it is located in Los Alamos County and in six counties west and southwest of Los Alamos County. The second cluster of childhood acute lymphoblastic leukemia does not include Los Alamos County and counties immediately adjacent to Los Alamos County. The cluster of acute lymphoblastic leukemia is located in the central-southwest part of the state with concentrations in Bernalillo, Cibola, Valencia, Socorro, and Dona Ana counties. Three counties in both detected statistically significant clusters are Bernalillo County, Cibola County, and Valencia County. In both clusters, Bernalillo County is the county that one should be most concerned with

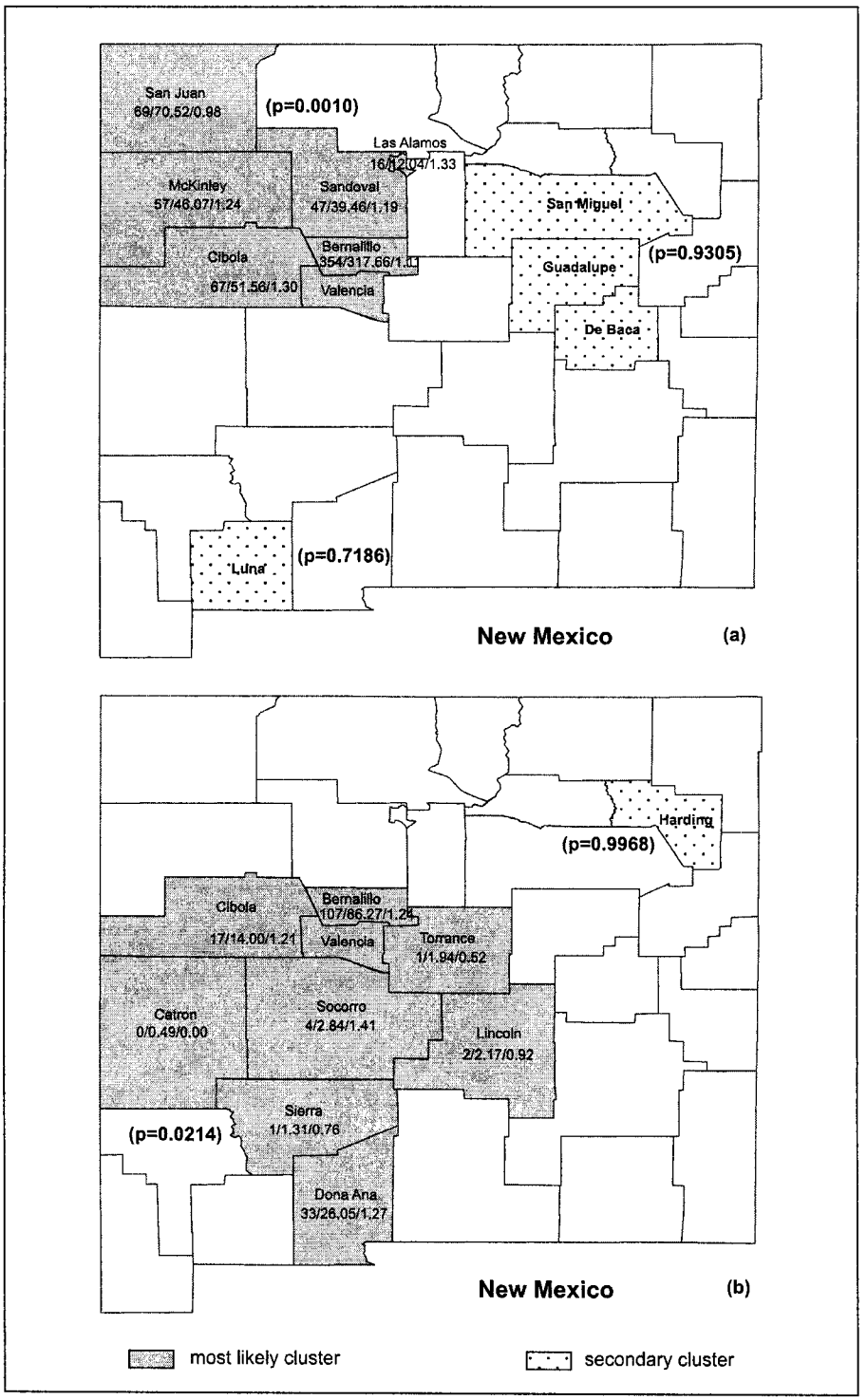

Figure 1. Childhood cancers with a statistically significant cluster in New Mexico (1973-97): (a) All childhood cancers combined; (b) Childhood acute lymphoblastic leukemia. (Note: Covariates used in the analysis included race, age group, and sex. The numbers next to each county name are: the number of observed cases/number of expected cases/observed to expected ratios in that county. The numbers for Cibola and Valencia counties are combined.)

because it contained most of the observed cases, and because most of the areas in the county are less than 150 km from Los Alamos. For both brain cancer and all leukemia cases, no cluster was detected.

It should be noted that in the two statistically significant clusters, the observed/expected ratios are relatively small. The observed/expected ratio is 1.14 for the statistically significant cluster of all childhood cancers, and the observed/expected ratio is 1.22 for the statistically significant cluster of acute lymphoblastic leukemias. Because these two clusters are statistically significant, their importance cannot be denied. But the magnitude of these clusters is not terribly alarming when the observed/expected ratios in the clusters are taken into consideration.

The author recognizes that the primary race ethnic groups in New Mexico are non-Hispanic whites, Hispanic whites, and American Indians, and there are few blacks in New Mexico. Rates of childhood cancer vary strongly by race in NM. It would be better to conduct the analyses based on these race-ethnicity groups in New Mexico. But there was simply not complete population data for the 25-year period available for the analyses. In this study, the race category 'white' included both non-Hispanic whites and Hispanic whites, and the race category 'other' is predominantly American Indians. Because the analysis results in this study are based on incidence rates adjusted by race (white, black, and other), sex, and age group, the resulting clusters are reflective of the demographic situation in the state .

Searching for causes responsible for these childhood cancer clusters is a very challenging task. In the literature, several recognized risk factors for explaining childhood cancer clusters include exposure to ionizing radiation in utero or during childhood, some congenital malformations (e.g., trisomy 21), and consumption of certain medications (e.g., chloramphenicol) (Laurier and Bard 1999, Little 1999). Other suspected risk factors include viral infection during pregnancy and/or childhood, maternal smoking, living near electromagnetic fields, food addictives, and exposure to industrial and agricultural chemicals (e.g., pesticides) and dusts during childhood, ionizing radiation, and viral infection (Carroquino et al. 1998, Laurier and Bard 1999, Little 1999, Kinlen 1995, Kinlen and Balkwill 2001). Ideally, all these risk factors and their relationships to the detected clusters should be examined. In addition, as the Los Alamos National Laboratory is proximate to counties where clustering was detected, future studies to examine the relationship between atmospheric testing of nuclear weapons and patterns of childhood cancer are indicated.

It is also possible that the clusters may be associated with different population change curves in different counties in New Mexico during the past three decades. To examine this possibility, future studies should be designed to consider these changes in relation to the viral infection hypothesis (Laurier and Bard 1999, Little 1999, Kinlen 1995, Kinlen and Balkwill 2001). So far, more than twenty independent studies have found evidences supporting the viral infection hypothesis although not all studies have confirmed the hypothesis (Laplanche and de Vathaire 1994, Kinlen 1994) and the biological mechanisms behind the hypothesis have not been fully understood. The degree of population change and migration is fairly different in different counties in New Mexico during the period from 1970 to 2000 (Table 2).

Sandoval County, a county immediately southwest of Los Alamos County, experienced the most population growth with four times more population in 2000 than in 1970. Valencia County came second and more than doubled its population during the 30 years. Valencia County is within both the most likely cluster of all childhood cancers and the most likely cluster of acute lymphoblastic leukemia. Sandoval County is in the most likely cluster of all childhood cancers. Other counties in either of the two most likely clusters all had population growth in the 30-year period (Table 2). Dona Ana County and San Juan County more than doubled their population over the 30 years. Socorro County saw its population grew more than 85% during the 30 years. Bernalillo County and McKinley County had over 70% population growth during the 30-year period. Cibola County and Los Alamos County only had modest population growth.

(Table 2 about here)

Not all counties with large population growth are within the statistically significant clusters, however. Among the eight counties that more than doubled their population during the 30-year period, four counties (Sandoval, Valencia, Dona Ana, and San Juan) are in the clusters and four counties (Torrance, Lincoln, Santa Fe, and Luna) are not (Table 2). This distribution gives a mixed picture about the relationship between childhood cancer clusters in New Mexico and population change, and no definitive conclusions can be drawn based on these results at this time.

The spatial cluster patterns elicited in this exercise hold only for county-level cancer incidence data available in the SEER public-access data set. Time was addressed only by adjusting the size of the population at risk. The patterns elicited did not rule out a link between atmospheric testing and childhood cancer, nor did they discount the idea that viral infection may play a role in childhood cancer clusters. It would certainly be worthwhile to test the viral infection hypothesis in relation to population change using data at a finer geographic scale (e.g., at the census tract level) so that more conclusive results may be obtained. An analysis at finer geographic scale, however, would require address-based geographic location data that are not available in the public domain. This type of analysis is thus left as a topic for future research. In addition, given the level of population changes that had taken place in the three decades, it is possible that several of the cancer incident case children living in the clusters were diagnosed with cancer shortly after moving to New Mexico from other states. In these cases, it is unlikely that local exposures or viral infections would be etiologically relevant for these cases. Clearly, more detailed individual data and different methods are needed to address issues related to this situation. This is another issue where further research is necessary. Should these data be examined with other space/time cluster methodologies, or should this exercise be repeated at different geographic scales, the data may yield different cluster patterns. Such efforts would be welcome in the effort to understand the underlying causes of childhood cancer.

Table 2. County population change in New Mexico from 1970 to 2000 (Data source: U. S. Bureau of the Census)

County Name	Pop1970	Pop1980	Pop1990	Pop2000	Net Change (1970-2000)	Percent Change (1970-2000)
Sandoval County	**17,492**	**34,400**	**63,319**	**89,908**	**72,416**	**414.0**
Valencia County	**20,468**	**30,768**	**45,235**	**66,152**	**45,684**	**223.2**
Torrance County	5,290	7,491	10,285	16,911	11,621	219.7
Lincoln County	7,560	10,997	12,219	19,411	11,851	156.8
Dona Ana County	**69,773**	**96,340**	**135,510**	**174,682**	**104,909**	**150.4**
Santa Fe County	54,774	75,519	98,928	129,292	74,518	136.0
San Juan County	**52,517**	**81,433**	**91,605**	**113,801**	**61,284**	**116.7**
Luna County	11,706	15,585	18,110	25,016	13,310	113.7
Socorro County	9,763	12,566	14,764	18,078	8,315	85.2
Sierra County	7,189	8,454	9,912	13,270	6,081	84.6
Bernalillo County	**315,774**	**420,262**	**480,577**	**556,678**	**240,904**	**76.3**
McKinley County	**43,208**	**56,536**	**60,686**	**74,798**	**31,590**	**73.1**
Taos County	17,516	19,456	23,118	29,979	12,463	71.2
Rio Arriba County	25,170	29,282	34,365	41,190	16,020	63.6
Catron County	2,198	2,720	2,563	3,543	1,345	61.2
Otero County	41,097	44,665	51,928	62,298	21,201	51.6
Chaves County	43,335	51,103	57,849	61,382	18,047	41.6
Grant County	22,030	26,204	27,676	31,002	8,972	40.7
San Miguel County	21,951	22,751	25,743	30,126	8,175	37.2
Cibola County	**20,108**	**30,347**	**23,794**	**25,595**	**5,487**	**27.3**
Eddy County	41,119	47,855	48,605	51,658	10,539	25.6
Hidalgo County	4,734	6,049	5,958	5,932	1,198	25.3
Los Alamos County	**15,198**	**17,599**	**18,115**	**18,343**	**3,145**	**20.7**
Colfax County	12,170	13,667	12,925	14,189	2,019	16.6
Curry County	39,517	42,019	42,207	45,044	5,527	14.0
Lea County	49,554	55,993	55,765	55,511	5,957	12.0
Mora County	4,673	4,205	4,264	5,180	507	10.8
Roosevelt County	16,479	15,695	16,702	18,018	1,539	9.3
Guadalupe County	4,969	4,496	4,156	4,680	-289	-5.8
Quay County	10,903	10,577	10,823	10,155	-748	-6.9
DeBaca County	2,547	2,454	2,252	2,240	-307	-12.1
Union County	4,925	4,725	4,124	4,174	-751	-15.2
Harding County	1,348	1,090	987	810	-538	-39.9

Note: Counties in bold are the counties in either of the two statistically significant clusters and with the number of observed cases exceeding the number of expected cases.

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