Spatial Distribution of Orofacial Cleft Defect Births in Harris County, Texas, and Radium in the Public Water Supplies: A Persistent Association?

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Abstract

Geospatial tools were used to evaluate radioactivity in drinking water and an association with cleft birth defects. From the use of a space-time clustering program (SaTScan), a significantly increased relative risk of 3.0 (95% CI, 1.8-4.3) for cleft births in northwest Harris County was previously reported for the period from 1990 through 1994. This cluster occurred in an area containing water wells with alpha radiation that exceeded allowed standards.

New data for a decade later (from 1999 through 2002) from the recently formed Texas Birth Defects Registry and concurrent data for radium in tap water from the Texas Commission on Environmental Quality made it possible to conduct a follow-up investigation. Rates of cleft birth defects were again significantly (P<.001) greater both in ZIP codes and census tracts with elevated radium concentration in drinking water. Adjustment for sex of newborn, maternal age, race, and educational achievement did not remove this association. A persistent pattern in two separate study periods makes the reported association more robust and noteworthy for the attention of Texas physicians.

Introduction

Orofacial cleft birth defects are some of the more common congenital anomalies. The incidence varies among investigations (depending on the data sources and the inclusion or noninclusion of stillbirth and abortions with the live birth totals). In Texas, during the period from 1999 through 2002, a total of 851 babies were born with cleft palate alone and 1563 with cleft lip, with or without cleft palate. Cleft palate alone had a rate of 5.87 per 10,000 births (95% CI, 5.47-6.26) and cleft lip had a rate of about 10.78 per 10,000 births (95% CI, 10.25-11.31).

The causes of cleft palate and cleft lip have not been firmly established. Current theory holds that cleft formation is a heterogeneous process; thus, defects are likely to result from a variety of causes, including genetic influences and environmental insults Several studies have reported that exposures to radiation involve teratogenic risks Exposure of animals to radium, in the phase of organogenesis comparable to that in humans, has been shown to result in abnormal and incomplete embryonic development Ritenouer found that maternal exposure to gamma radiation in pregnancy resulted in preimplantation death, growth retardation, and central nervous system defects. Brent reported growth retardation, microcephaly, and mental retardation in the offspring of women who were treated with therapeutic radiation for medical reasons before knowing they were pregnant.

Studies of atomic bomb survivors in Hiroshima and Nagasaki, Japan, indicated that the risk of malformations was greatest between 8 to 15 weeks of gestation. The major defect in children born after the A-bomb was decreased size and shape of the cranium. Domestic exposure to radiation has also been implicated in the development of birth defects, including cleft defects. An epidemiological study conducted in the 1950s in New York found an elevated rate of malformations, specifically cleft malformations, in areas underlain...
by uranium-bearing igneous rocks. More recently, studies in the former East Germany reported a 9.4% increase in the rates of cleft malformations subsequent to the meltdown of the Chernobyl reactor in 1986. In all, both ionizing and nonionizing radiation have been shown to impair animal and human reproductive capacity.

Uranium-bearing formations occur in Texas and Mexico and coincide geographically with the recharge area of the Gulf Coast ground water aquifer. While these radioactive deposits exist at depth, they could be brought to the surface in connection with human activities. Among others, the presence of uranium → radium → radon isotopes could be anticipated in the production water and wastewater associated with hydrocarbon exploration.

In the late 1980s and 1990s, urban development began spilling rapidly into northwest Harris County, Texas. Some of the previous land uses might not have been fully compatible with this urban advance and the development of groundwater wells. During the 1980s and early 1990s, elevated concentrations of radium-226 and radon-222 were reported in several wells in northwest Harris County, Texas, by Cech and coinvestigators. Radium concentrations, up to 22 pCi/L, were found in the tap water near a major hydrocarbon exploration field. Radon concentrations, as great as 2,000 pCi/L, were also detected in the same area.

That elevated domestic level radiation continues to be an issue in Harris County is evident from a 2003 monograph by the National Resources Defense Council, which stated that the average radon levels in the Harris County public water supplies are twice the proposed national standard of 300 pCi/L. While radon is not routinely monitored in the public water supplies, the US Environmental Protection Agency (USEPA) has established 5 pCi/L as the maximum contaminant level (MCL) for radium (combined Ra-226 and Ra-228 isotopes). In this regard, the Texas Commission on Environmental Quality (TCEQ) registered that during the period from 1999 through 2002 as many as 18 different public water supply systems in Harris County were still in violation of this combined MCL.

In the same part of Harris County, our earlier study reported a cluster of significantly greater-than-expected orofacial cleft defect births for the period from 1990 through 1994 (with the relative risk = 3.0, P=.043). Twenty-two babies were born in this period with cleft defect, against the expected seven, in an area of 4 square miles. In that study, Geographic Information System (GIS) methods were used to map home addresses of cleft births and all births in Harris County according to the data from the Bureau of Vital Statistics. Those data were analyzed by using the space-time clustering program SaTScan, developed by the National Cancer Institute. The distribution was compared with historical data on radium and radon in the water collected by the first author.

**Methods**

The Texas Birth Defects Registry, which became operational in the 1994s, has data from 1999 through 2002. This new (and presumably better verified) data set made it possible to reexamine the spatial distribution of cleft defects for consistency of an association with concurrent new data on distribution of waterborne radium. The present study population consisted of births nearly one decade later than our earlier study. Concurrent new data on radium concentrations in household water supplies from 1999 through 2002 were obtained from TCEQ. Data on the reference population of all births in Harris County were obtained from the Texas Center for Health Statistics.

Fetal experience in the first trimester is the key to the formation of orofacial cleft birth defects. To take into account this developmental stage vulnerability and to maintain temporality for the hypothesized exposure-effect relationship, the radium distribution record was restricted to observations made from January 1, 1999, through June 30, 2002, and orofacial cleft birth defect records were restricted to births between July 1, 1999, and December 31, 2002.

The locations of public water supply wells were geocoded and mapped by latitude and longitude with MapInfo software. Combined radium (Ra-226 and Ra-228) concentrations in community well water in Harris County, Texas, were mapped (Figure 1). A contour map of radium concentrations was constructed by using SURFER50 (step not shown) and overlaid with maps of Harris County ZIP codes and census tracts. These geographic polygons were dichotomized as low radium (<3 pCi/L) and elevated radium (≥3 pCi/L). The MCL for combined total radium is 5 pCi/L. However, the threshold of 3 pCi/L was used to classify zip codes and census tracts for radium exposure, because radium found in Harris County is primarily in the form of Ra-226, which makes up roughly 60% of the total combined radium concentrations. The same rationale and the same threshold concentrations were used in the earlier studies.

Census tracts and ZIP codes corresponding to the exposure dichotomy were identified and mapped by using
MapInfo shape files for the year 2000 (Figure 2, a and b).

Residential addresses of orofacial cleft defect births were geocoded by using MapMarker software. ZIP codes stated in the address and the ZIP codes generated from geocoding were verified for consistency by using MapMarker and the Postmaster General's address database system. Most (98.4%) of the addresses could be accurately geocoded to a point location; the remaining small proportion (1.6%) could not be accurately geocoded due to missing or incomplete address information. The geocoded addresses were mapped with MapInfo.

The SaTScan software was used to investigate spatial clustering of cases, and multivariate models were used to adjust cleft birth rates for demographic covariates. A longitude and latitude grid for Harris County that was constructed contained square "blocks" measuring 0.01 degrees (approximately 0.6 miles) on each side. This allowed us to count the number of cases vs noncases within each "block." The "block" rates were modeled by using a Bernoulli clustering algorithm, which progressively grouped "blocks" with elevated rates adjusting for the inhomogeneity of the background population.

Case enumeration of orofacial cleft defect births was aggregated for the 4-year period of this study, and rates by ZIP codes and census tracts per 10,000 live births were calculated by using total live births by ZIP codes and census tracts as denominators, respectively. Maps displaying these rates were constructed by using MapInfo (Figure 3, a and b).

The Stata generalized linear model procedure was used to compare the differences in rates of cleft birth defects in ZIP codes and census tracts whose water supplies contained <3 pCi/L and ≥3 pCi/L of radium. A multivariate generalized linear model adjusted for the potentially confounding variables of sex of newborn, race of mother, age of mother, and level of educational achievement of mother (Tables 1 and 2).

**Results**

Figure 1 shows that total radium at concentrations of ≥5 pCi/L existed in 18 subdivisions and at concentrations of ≥3 pCi/L in 41 subdivisions. The geographic distribution of radium measurements generally confirmed the presence of water supply systems with elevated radium in northwest (and some in northeast) Harris County – similar to levels reported in the 1980s and 1990s, with only slightly lower peak concentration (22 pCi/L vs 14.3 pCi/L), but still about three times in excess of the allowed concentration.

There were 300 reported births with orofacial cleft defects and 207,300 reported live births with maternal residential addresses in Harris County, Texas, during the study period, the mean annual rate being 14.47 cleft defect births per 10,000 live births. More than one-half (56%) of the cleft birth defects cases were males. Twenty eight percent of the cases were white, 12% black, and 53% Hispanic. Elevated rates by ZIP codes and census tracts were observed in northwest and northeast Harris County, in a pattern similar to that of observed elevated radium concentrations (Figure 3, a and b).

The mean rate and standard deviation (± SD) per 10,000 live births for ZIP codes classified as having elevated radium (≥3 pCi/L) were 19.59 ± 7.61. The mean rate and SD per 10,000 live births for zip codes classified as having low radium (<3 pCi/L) were 13.48 ± 8.6, a significant reduction (P<.001). Subsequent adjustment for sex of newborn, race of mother, age of mother, and educational level of mother, as potentially confounding variables, did not diminish the statistical significance (P<.001) of the radium concentration in household water supplies (Table 1).

The mean rate and SD per 10,000 live births aggregated by census tracts with elevated radium (≥3 pCi/L) were 15.55 ± 16.86. The mean rate and SD per 10,000 live births for census tracts having low radium (<3 pCi/L) were 14.36 ± 20.65, again a significant reduction (P<.0001). Adjustment for confounders did not change this finding (Table 2).

The SaTScan Bernoulli analysis indicated the most probable cluster was located in northwest Harris County, with a relative risk of 8.6; however, the P value was not statistically significant (P=.163). This cluster was in a similar location to that observed 10 years earlier. The shift in location corresponded to the direction of population spread.

**Discussion**

In the present study, the mean annual prevalence rate of cleft defects was 14.47 per 10,000 live births from 1999 through 2002. This rate was slightly lower than 16.4 per 10,000 births for Texas overall and slightly greater than 13.1 per 10,000 births for Harris County as reported by the Texas Birth Defects Registry for the same time span. These small differences may be due to the fact that this study calculated rates on the
basis of births that took place in Harris County with maternal residences in Harris County as the reference population, while the registry uses all births to mothers who listed Harris County as their residence regardless of delivery site. Importantly, the rates of cleft defect births in this study, as well as in the earlier studies, showed marked and significant geographic variation within Harris County.

Cech and coinvestigators previously (in the middle 1980s and early 1990s) found that the maximum radium-226 in Harris County was 22 pCi/L. The maximum combined radium reported by TCEQ for Harris County from 1999 through 2002 was still high (14.3 pCi/L, against MCL = 5 pCi/L), and the geographic distribution of the water wells with elevated radium (Figure 1) was similar to the studies conducted a decade earlier.

The mean annual prevalence rate of cleft defects was 19.59 per 10,000 live births for ZIP codes classified as having elevated radium concentrations (≥3 pCi/L). This rate was more than one-third greater (P<0.001) than the mean annual prevalence rate of 13.48 per 10,000 live births observed in ZIP codes classified as having low radium concentrations (<3 pCi/L). The difference in cleft rates by ZIP codes dichotomized for radium exposure persisted after adjustment for the potential confounders: sex of child, mother's age, race, and level of education. A similar trend was observed in census tracts with a prevalence rate of 15.55 per 10,000 live births for census tracts classified as having elevated radium concentrations (≥3 pCi/L) and a significantly reduced (P<0.001) rate of 14.36 per 10,000 live births observed in census tracts with low radium concentrations (<3 pCi/L). This difference in rates by census tracts also persisted after adjustment for potential confounders.

It is biologically plausible that exposure to radium constitutes one of several potential factors that causes the development of cleft birth defects. In living tissue, radioactive ionization can damage chromosomes or other cellular structures, which can result in abnormal cell proliferation and cell death. Chronic human exposure to Ra-226 has been associated with bone sarcomas and head carcinomas, and chronic exposure to Ra-228 has been associated with bone sarcoma. The role of radium in birth defects has not been studied as extensively. However, radium's interference with bone formation in the animal embryo has been documented; the role of radium-228 in bone sarcoma; and especially their subsequent decay progenies, like isotopes of polonium (Po-210) and lead (Pb-210), follow calcium uptake into the fetal skeleton during bone formation; this may lead to the flawed fusion of skeletal components resulting in cleft and other structural defects.

A strength of the present study was the application of GIS methods to map cleft defect births in relationship to attributes of the natural environment. The success rate for geocoding residential addresses of cleft birth defect cases was 98.4%, well above the minimum geocoding address match rate of 90% acceptable in the literature. The residential address latitude and longitude of the reference population were provided by the Texas Center for Health Statistics by use of the Centrus software. The latitude and longitude of groundwater sources of public water supplies were provided by TCEQ, using Global Positioning System methods of geocoding.

This study used both census tracts and ZIP codes as geographical units of analysis. Census tracts are defined as "small, relatively permanent geographic entities within counties (or the statistical equivalents of counties) delineated by a committee of census data users;" Census tracts usually consist of between 2500 and 8000 residents. A ZIP code is defined as a "five-, seven-, nine-, or eleven-digit code assigned by the US Postal Service to a section of a street, a collection of streets, an establishment, structure, or group of post office boxes, for the delivery of mail." There is no consensus on which unit, a ZIP code or a census tract, is preferable for a GIS type of study. One difficulty other investigators have experienced with the use of either ZIP codes or census tracts was the change over time in boundaries, with ZIP codes being added or discontinued in nondecennial years. This can lead to incorrect and inconsistent assignment of ZIP codes and census tracts to the cases, reference population, and water sources. However, in our study, we geocoded the latitudes and longitudes and assigned ZIP codes and census tracts using the same MapInfo Census 2000 database, thus maintaining precision and consistency.

Census tracts are generally smaller in population counts, with large variation in area size. Therefore, larger census tracts may visually dominate thematic maps, and rates may be easily inflated or deflated due to small numbers of cases. On the other hand, ZIP codes are more homogeneous in size; hence, thematic maps are not as visually misleading. In addition, the number of live births per ZIP code is higher compared with the number per census tract, because census tracts have approximately one-eighth the population of ZIP codes. Smaller population sizes often result in unstable prevalence rates for relatively infrequent events like cleft birth defects in the census tracts, while larger ZIP code populations result in more stable rate estimates. Thus, the results of analyses that use census tracts can be misleading. However, in our study we found similar results using either ZIP codes or census tracts as geographical units of measure.
Many studies use census data to impute confounding variables, which may not accurately characterize individuals over time. Also, the potential exists for spatial-temporal mismatches between census-derived reference data or ZIP code-derived case data.\textsuperscript{64} This was avoided in our study, and accuracy was maintained by the use of individual-level measures provided by the Texas Center for Health Statistics. These population measures could, therefore, be extended to analyses at either the census tract or ZIP code level.

Compared with our previous work, this new study made use of the most recent radionuclide data obtained from TCEQ and the most recent cleft birth defect cases from the Texas Birth Defects Registry. The registry employs active surveillance by trained workers who visit hospitals and birthing centers to abstract information from medical records. A comparison of the Bureau of Vital Statistics birth defects data with the Texas Birth Defects Registry as the standard found that the Vital Statistics records were less accurate indicators of cases than were the registry records in 1999-2000.\textsuperscript{65} However, for cleft defects the congruity was more than 80\%, which was better than for other birth defects.

The study had several limitations. Concentrations of radium were those of water wells serving residential subdivisions. It is not clear how much difference there would have been if radium had been measured at the kitchen tap, but it is unlikely that this would have eliminated the observed strong association. Another limitation was that competing risk factors, such as maternal smoking, substance abuse, and nutritional deficiencies, could not be measured. No data were available on parental occupation. Misclassification may also be due to differences between the residence at birth and at conception of the index cases. However, this would have been true for all births. Also unknown is how many birth defect cases and live births might have been lost to spontaneous or elective abortion. There were no known prior clusters of genetic syndromes that may contribute to elevated rates of orofacial cleft defect births in northwest Harris County. While genetic clusters were beyond the scope of this study, it is difficult to envision and identify such distinct genetic clusters in a cosmopolitan population of the Greater Houston/Harris County, with a multiracial population. However, adjustment for race of newborn did not eliminate significant association between cleft defects and radium in tap water.

Compared with the previous study by Cech and coinvestigators,\textsuperscript{4} radon gas exposure data were lacking. Radon is not monitored under the Safe Drinking Water Act and, thus, systematic official agency records do not exist. Measuring household-level radium or radon exposure would have required funding and technical resources that were not available for this study. Our previous studies took advantage of historical radon data collected in separate research investigations by the first author.

These findings should be regarded as a valuable first-step approach in the evaluation of environmental radioactivity in drinking water and the risk of orofacial birth defects. Other factors may play a role in this pattern and are studied further. On the other hand, while geographical patterns alone are insufficient to conclude that elevated radium levels in household water supplies are causally related to the occurrence of cleft birth defects in Harris County, Texas, the association observed in this study was consistent with previous reports in Harris County;\textsuperscript{47} biologically plausible and consistent with previous animal and human research,\textsuperscript{20,26,31,32,34,59} temporally consistent; and defect-specific. The investigators are proceeding with an incident-matched, case-control study protocol that is expected to ascertain direct biomarkers of individual exposures, competing risk factors, and confounders.

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**Table 1**

Generalized linear model analysis of annual prevalence rates of cleft birth defects by ZIF code, Harris County, Texas, 1999–2002 (ZIF code rates = Radium + Gender + Ethnicity + Age + Education).

| Variable* | Coefficient | Standard Error | Z     | P>|Z| | 95% Confidence Interval |
|-----------|-------------|----------------|-------|------|------------------------|
| Radium = 1 | 0.69        | 0.03           | 19.46 | <0.01 | 0.57 (0.81) |
| Gender = 2 | -0.05       | 0.02           | -2.80 | 0.01 | -0.10 (-0.02) |
| Ethnicity = 2 | 2.32 | 0.03           | 78.04 | <0.01 | 2.19 (2.45) |
| Ethnicity = 4 | 2.32 | 0.03           | 78.04 | <0.01 | 2.19 (2.45) |
| Education = 2 | 0.27        | 0.03           | 11.01 | <0.01 | 0.18 (0.36) |
| Education = 4 | 0.27 | 0.03           | 11.01 | <0.01 | 0.18 (0.36) |
| Constant | 15.42 | 3.11 | -46.60 | <0.01 | 10.23 (15.64) |

*Fertilized was coded as 0 = Low (<13 ml); 1 = Elevated (13+ ml).
**Gender was coded as 1 = Male; 2 = Female.
***Ethnicity was coded as 1 = White; 2 = Black; 3 = Hispanic; 4 = Other.
****Education was coded as 1 = Less than High School; 2 = High school or greater.

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**Table 2**

Generalized linear model analysis of annual prevalence rates of cleft birth defects by census tract, Harris County, Texas, 1999–2002 (Census tract rates = Radium + Gender + Ethnicity + Age + Education).

| Variable* | Coefficient | Standard Error | Z     | P>|Z| | 95% Confidence Interval |
|-----------|-------------|----------------|-------|------|------------------------|
| Radium = 1 | 0.04        | 0.19           | -0.64 | >0.10 | 1.21 (1.42) |
| Gender = 2 | -0.24       | 0.09           | -2.80 | 0.01 | -0.42 (0.04) |
| Ethnicity = 2 | -0.01 | 0.19 | -3.01 | <0.01 | -0.14 (-0.02) |
| Ethnicity = 4 | -0.01 | 0.19 | -3.01 | <0.01 | -0.14 (-0.02) |
| Education = 2 | -0.70 | 0.20 | -3.01 | <0.01 | -1.65 (1.80) |
| Education = 4 | -0.70 | 0.20 | -3.01 | <0.01 | -1.65 (1.80) |
| Constant | 15.42 | 3.11 | -46.60 | <0.01 | 10.23 (15.64) |

*Fertilized was coded as 0 = Low (<13 ml); 1 = Elevated (13+ ml).
**Gender was coded as 1 = Male; 2 = Female.
***Ethnicity was coded as 1 = White; 2 = Black; 3 = Hispanic; 4 = Other.
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**Figure 1**

Radios concentration in public water supplies (groundwater only), Harris County, Texas, January 1999 through June 2002.
Figure 2a
Harris County (a) ZIP codes and (b) census tracts classified by radium threshold dichotomy as low (<3 pCi/L) and elevated (>3 pCi/L).

Figure 2b

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