Spatial Distribution of Orofacial Cleft Defect Births in Harris County, Texas, 1990 to 1994, and Historical Evidence for the Presence of Low-level Radioactivity in Tap Water

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Background: While both ionizing and nonionizing radiation are known to impair human reproductive capacity, the role of low-level domestic radiation continues to be an unsettled issue.

Objectives: We examined the geostatistical distribution (residential longitude and latitude) of orofacial cleft birth cases adjusted for the underlying population distribution. Furthermore, we examined the cleft birth rates enumerated by zip codes for possible associations with levels of radium and radon in drinking water.

Methods: Cleft births and unaffected live births in Harris County, Texas, from 1990 to 1994, were geocoded by residential addresses and tested for spatial clusters using the space-time clustering program SaTScan. Historical sample data on local variations in water quality facilitated the assessment of the association of orofacial cleft defect births with low-level radiation exposure.

Results: A cluster of significantly greater than expected numbers of cleft defect births was identified in northwest Harris County, (relative risk = 3.0, \( P = 0.043 \)), where the presence of elevated levels of radium (>3 pCi/L) and radon (>300 pCi/L) in the tap water has been known since the 1980s.

Conclusions: Despite the ecological design of the study, lacking individual exposure measurements for cleft birth residences, there was strong suggestive evidence of an association between elevated radiation levels in tap water and elevated cleft birth prevalence rates by zip codes. Attention of physicians is invited to environmental causes as potential risk factors for orofacial cleft. This would aid in genetic counseling and the development of future preventive measures.

Key Words: orofacial cleft, low-level radiation, drinking water, geographic information system (GIS) methods.

The term “facial clefting” refers to a spectrum of defects which involve the upper lip, the palate, or both. The exact cause(s) of orofacial cleft development has not been resolved. It is currently theorized that facial clefting is a heterogeneous process resulting from a variety of causes, including genetic factors and environmental insults, with possible environmental and genetic interactions.

Key Points
- Rapid urban expansion involves the risk of encroachment into areas where previous land uses might not have been fully compatible with the development of residential water wells.
- Attention of physicians is invited to radium and radon as unsuspected and unnecessary health risk factors in some tap water.
- A cluster of significantly greater numbers of cleft defect births relative to the total numbers of live births has been documented in the northwest part of Harris County, Texas, where elevated levels of radium and radon have been known since the 1980s.
- Geographic areas with a high probability of exposure to elevated levels of domestic radiation need to be targeted for studies of cleft and other cranioskeletal birth defects.
serum folate and low vitamin B₆ and B₁₂ status. Orofacial cleft N-acetyltransferase phenotype, maternal smoking, and medication use was also investigated, with negative results. In all, it still remains to be seen whether these factors and their interactions are a sufficient explanation for cleft etiology, and the need for further research is apparent. Understanding environmental triggers is important, because the exposures are preventable.

Many authors agree that in utero exposures to ionizing radiation involve teratogenic risks. 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 the children born after the A-bomb was a decrease in head size accompanied with mental retardation. Studies in the former East Germany reported a 9.4% increase in the rates of cleft deformities between 1987 and 1989, subsequent to the meltdown of the Chernobyl reactor in 1986.

Brent reported growth retardation, microcephaly, and mental retardation in the offspring of women, who were treated with therapeutic radiation for various medical reasons and before knowing that the patient was pregnant. Ritenour found that maternal exposure to doses above 15 rems early in pregnancy resulted in preimplantation death, growth retardation, and central nervous system defects.

Domestic-level radiation has been implicated in the development of birth defects, including cleft defects, as far back as the 1950s. A study in New York State found an elevated rate of malformations in areas underlain by uranium-bearing rocks. Rates of orofacial cleft were 33% greater than in areas classified as unlikely for exposure to uranium decay products. However, no data on actual concentrations of radioactive isotopes in the drinking water supplies were available. This was a weakness of an otherwise pioneering study.

In all, while both ionizing and nonionizing radiation were shown to impact human reproductive capacity and produce birth defects, with few exceptions, the data were derived from studies involving cases of acute exposure and high doses. There are limited data available regarding reproductive and teratological consequences associated with domestic levels of radiation exposures and an obvious need to reduce the uncertainty.

Present Study

During the 1980s and early 1990s, elevated concentrations of radium-226 and radon-222 in groundwater wells and tap water were reported in Harris County, Texas, particularly in the northwest. Radium concentrations, as great as 15 pCi/L, were found in the water, in an area near a major hydrocarbon field. Radon concentrations, as great as 2,000 pCi/L, were also reported in the water (Figs. 1 and 2). In contrast, the part of Harris County supplied by surface water had no radionuclide concentrations above acceptable standards. The availability of these historical data and the pres-
ence of regional variations in concentrations of radium and radon in tap water created an opportunity in the present study to assess the association of cleft birth defects with low-level radiation exposure.

**Methods**

This was a medical-geographic study of the distribution of cleft palate and cleft lip incidence in infants born to families residing in Harris County, Texas, between 1990 and 1994. Texas birth certificates were the source of cleft palate/cleft lip deformity information. Residential addresses of cases and live births were geocoded by longitude and latitude, using StreetInfo and MapMarker software by MapInfo, Inc. (Fig. 3).

To investigate the spatial clusters of orofacial births in Harris County, Texas, we used the space-time clustering program SaTScan. A longitude and latitude grid for Harris County was constructed containing square “blocks” measuring 0.01 degrees (approximately 0.6 miles) on each side. This allowed counting the number of cases versus noncases within each “block.” The “block” locations were modeled using a Bernoulli clustering algorithm, which progressively grouped excess density clusters and adjusted the spatial density of the cases for the underlying inhomogeneity of the background population (Fig. 4).

The orofacial defect births were aggregated by the Harris County zip codes to calculate rates per 10,000 live births. The independent variables were the previously reported radionuclide concentrations in water supplies in Harris County, collected during the period 1987 to 1992. (Figs. 1 and 2). Recently obtained data for the period 1999 to 2002 from the Texas Commission for Environmental Quality (TCEQ) were geocoded and plotted by the authors (data not shown), indicating that the radiation levels in the well water had generally not diminished.

Concentrations of radium-226 were dichotomized as “<3 pCi/L” and “≥3 pCi/L.” The current maximum contaminant level for total radium is 5 pCi/L (isotopes of Ra-226 and Ra-228 combined). Concentrations of radon-222 were dichotomized as “<300 pCi/L” and “≥300 pCi/L,” the latter being the limit proposed by the Environmental Protection Agency for public water supplies. Zip codes corresponding to either category of potential exposure were appropriately indexed. The boundaries of Harris County 1990 zip codes were available from MapInfo.

The differences in rates of cleft birth defect by zip codes located in the areas classified as <3 pCi/L and ≥3 pCi/L of radium-226 were compared (Table 1). Analyses were repeated for the radon-222 dichotomies of <300 pCi/L and ≥300 pCi/L (Table 2). Multivariate analyses of the dichotomies were repeated, adjusting zip code rates for potentially confounding variables, including (a) population density, (b) racial and ethnic composition, (c) per capita income, (d) level of educational achievement, and (e) ratio of white-to-blue
collar workers. The data for 1990 zip codes were obtained from TargetPro digital database available from MapInfo.

Results
There were 167 births with orofacial defects with a reported residential address in Harris County for the period 1990 to 1994, resulting in a mean annual rate of 5.7 per 10,000 live births. Results of a Bernoulli spatial analysis identified a cluster of 22 cases, compared with a background noncase population of 12,588, centered at -29.969 N, 95.560 W, with a radius of approximately 5 miles (8 km). On the Harris county map, this cluster coincided with the intersection of four major highways: 290 and 249 going out of Houston to NW, and highway 6 and beltway 8 encircling Houston from the NW. This area is marked on Figure 4 as an area of significantly increased risk for cleft defect births. The expected number of cases, adjusted for the number of live births in this area, was 7.3, resulting in a relative risk of 3.0 (95% CI (1.8, 4.3), P = 0.043). The clustering algorithm did not identify any other clusters where the relative risk of the adjusted case density significantly exceeded that of noncases.

Zip codes with the highest rates of cleft defect births (up to 39.5/10,000 live births) in northwest Harris County spatially coincided with the area where elevated concentrations of Ra-226 and Rn-222 have been known to occur since the 1980s. Table 1 shows that the mean annual rates for cleft defect births (14.6/10,000) for areas with Ra-226 ≥3 pCi/L were 2.70 times greater (95% CI 1.84, 3.54) compared with 5.4/10,000 for areas with Ra-226 <3 pCi/L. This difference was highly significant (P < 0.001). We subsequently adjusted cleft rates for potential confounding variables. None of the covariables were significantly associated with cleft rates and the adjustment failed to diminish the statistical significance of radium concentrations in domestic water.

Table 2 shows that the mean annual rates for cleft defect births in Harris County were 9.3/10,000 live births in zip codes which were classified as having elevated radon 222. This was 1.7 times greater (95% CI 1.08, 2.31) compared with 5.5/10,000 in zip codes with Rn-222 concentrations below 300 pCi/L. This difference was significant (P < 0.05) and, as with radium, the adjustment for potentially confounding variables did not diminish the significance of radon concentrations.

Discussion
The median rate of cleft birth defects observed for Houston/Harris County, Texas, for the period between 1990 and 1994, was 4 per 10,000 live births and the mean rate was 6 per 10,000 live births. These statistics were in the same range as rates reported by other investigators. However, within the study area, rates of cleft defects exhibited significant vari-
Two to three decades ago, the area where the spatial cluster of cleft defect births was observed was sparsely populated, and the principal activities in northwest Harris County traditionally were rice farming and hydrocarbon exploration. In the late 1980s and 1990s, urban development began spreading rapidly into this area and this growth continues. Between 1991 and 2000, Harris County, Texas, experienced a 20.7% increase in population, and the “Houston Energy Corridor” extended northward.

Due to this urban expansion, many groundwater wells were drilled in northwest Harris County to accommodate the need for public and private water supplies. Some of the previous land uses might not have been fully compatible with this urban advance. It was discovered, for instance, that the benzene concentration in one of the public water wells in northwest Harris County, south of the City of Tomball, was 11 times greater than the maximum allowed under the Safe Drinking Water Act.

Furthermore, elevated concentrations of radium-226 and radon-222 were reported in some municipal utility districts in this part of Harris County as far back as 20 years. Data gathered by Brock in 1984 indicated that at least 12 municipal utility districts in northwest Harris County violated standards with respect to radium in the public drinking water. Cech and coworkers gathered further data on the distribution of radium-226 in the water and added radon-222 measurements in Harris County and other parts of Texas.

Gentry and coworkers in New York State reported that cleft birth defect rates varied, depending on the likelihood of radioactive being present in the drinking water. The rates of cleft defects ranged from 12 to 16 per 10,000 live births, with the lower end of the range observed in areas classified as “unlikely” for radiation exposure via water, and the higher end of the range observed in areas classified as “probable” for radiation exposure via water.

In the present study in Harris County, Texas, the mean annual incidence rate of cleft defects was 15 per 10,000 live births for a group of zip codes situated in the area with Ra-226 concentration in drinking water ≥3 pCi/L. This was significantly greater than 5 per 10,000 live births observed in parts of Harris County with no appreciable concentrations of radon. The differences in cleft rates dichotomized for both radium and radon concentrations were highly significant (P < 0.001 and P < 0.05). These differences persisted after adjustment for other factors, such
Table 1. Mean annual incidence rates of cleft birth defects by radium-226 concentrations in the domestic water; univariate and adjusted for potentially confounding variables, Harris County, Texas, 1990–1994

Descriptive statistics
Dependent variable: mean annual rate

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Tests of between zip code effects
Dependent variable: mean annual rate

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Tests of between zip code effects
Dependent variable: mean annual rate

Where covariates were: Occupation = ratio of white to blue collar workers per zip code; per capita income, U. S. dollars; education, percent < 9 years of school completed; percent white population; percent black population; percent Hispanic population; percent Asian population.

Table 2. Mean annual incidence rates of cleft birth defects by radon-222 concentrations in domestic water; univariate and adjusted for potentially confounding variables, Harris County, Texas, 1990–1994

Descriptive statistics
Dependent variable: mean annual rate

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Tests of between zip code effects
Dependent variable: mean annual rate

Where covariates were: Occupation = ratio of white to blue collar workers per zip code; per capita income, U. S. dollars; education, percent < 9 years of school completed; percent white population; percent black population; percent Hispanic population; percent Asian population.
as differences in per capita income, educational achievement, proportion of white-to-blue collar occupations, and ethnicity.

It is biologically plausible that radioisotopes of uranium (Ra-226 and Rn-222) were a contributing factor in the development of cleft birth anomalies in northwest Harris County. Radiation is known to produce spermatotoxic and mutagenic effects. Dixon included both ionizing and nonionizing radiation among agents capable of impairing human reproductive capacity, both male and female. Exposure to ionizing radiation was reported to produce microcephaly, mental retardation, growth retardation, and Down syndrome. Animal studies also reported developmental malformations, including meningocoele, spina bifida, eye defects, tail defects, and edema in irradiated laboratory mice. Researchers interpreted the mechanism of radiation-induced teratogenesis as resulting from direct cell destruction, with residual DNA damage.

In our opinion, there is another mechanism by which uranium decay products may contribute to structural birth defects. Radium is a known "bone seeker." Being biologically analogous to calcium, radium competes for calcium sites in the growing fetal bone matrix. According to Mays and coworkers, most of the radium atoms are deposited in the growing areas, which makes the developing embryo particularly sensitive.

Radon-222 gas is the first progeny of decaying radium. Mays and coworkers measured radon retention in the bones of radium-injected beagles. They reported that practically all radon retention occurred in bone crystals and not in fat or other organic material, and that radon recoiled during radium disintegration, which caused damage to the bone structure. Significantly, Mays and coworkers have shown that the highest fractional radon retention (up to 22%) occurred in the jawbone and calvarium. These authors indicated that fractional radon retention after exposure was similar in rats, dogs, and man.

An important paper by Purnell and coworkers pointed out that in early gestation, the fetal skeletal structure is primarily cartilaginous, and calcium uptake increases markedly during the bone formation process. Radon-222 is too short-lived to be significantly transferred across the placenta to the fetus. However, radon decay progenies, isotopes of lead (Pb-210) and polonium (Po-210), will follow calcium into the fetal skeleton during maturation. This mechanism may explain defective fusion of skeletal components, including possibly cleft and other structural defects.

In our investigation using geospatial methods, we recognized the importance of scale. Geographical referents were assigned by latitude and longitude to addresses of cleft defect births, which allowed testing for spatial clusters using SatScan. In subsequent steps, rates per 10,000 live births were calculated for 1990 zip codes and compared by zip codes with the likely versus unlikely presence of radiation in tap water. Further analyses were adjusted for potentially confounding effects of demographic variables, also by 1990 zip codes. In a parallel study carried out by our group, cleft defect births were aggregated by 1990 census tracks instead of zip codes. This produced similar results, albeit with greater variation in the incidence rates due to smaller numbers of both cleft defect births and overall live births in census tracks compared with zip codes. This study will be detailed in a subsequent communication.

Today, Texas has one of the best birth defect registries in the country, but the registry has a relatively recent history. At this writing, birth defect registry data in Harris County were available for only 3 years, from 1999 to 2002. This registry was not in existence during the years when the radiation data was collected in a series of scientific studies by Brock and by Cech and coinvestigators.

The Vital Records data on birth defects and the Birth Defect Epidemiology and Surveillance Branch Registry data are not identical. The Registry utilizes active surveillance by trained workers, who physically visit delivery facilities and abstract medical records. Marenco calculated the sensitivity of the Bureau of Vital Statistics (BVS) data in recording selected birth defects, using the Texas Birth Defect Registry as the standard. For 1999 to 2000, the BVS records on birth defects were less accurate than the registry records. However, for cleft lip and palate, the concordance was 86% of the time. This was better than for other birth defects.

The present study shares some of the limitations typical of retrospective ecological studies. There were no direct radiation measurements of tap water in the case households, but the measurements were extrapolated from the data we obtained for the distribution systems. In addition, residential migration patterns within the study area, or into and out of the study area, were not evaluated. We believe that misclassification error by residence at birth versus conception would have been distributed evenly throughout the study area and not have affected the relative differences between the areas of lower versus higher concentrations of radionuclides. Still further, there were no known prior clusters of genetic syndromes that may contribute to elevated rates of orofacial cleft defects 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 such as that of the Greater Houston/Harris County, with a multiethnic and multiracial population. However, multivariate analyses indicated that race/ethnicity was not a significant factor associated with cleft birth rates.

With these limitations, the existence of historical data on Ra-226 and Rn-222 was a major strength, and considered to overcome the compromise of using older BVS records for cleft births for 1990 to 1994. It is our opinion that the underreporting on cleft births in BVS records would have been distributed uniformly within Harris County and would minimally change the relative differences in rates within the study area.

The radiation issues continue to exist in northwest Harris County, but the data quality reported by the public utilities
for years matching the birth defect registry record (1999–2002) was not an improvement over the data first reported in Harris County. The Houston/Harris County monitoring and reporting system was criticized in a 2003 by the Natural Resources Defense Council.73 Until 2003, the test protocol and regulatory compliance limits for radionuclides in drinking water were determined by samples taken from a vaguely defined "representative point to the water distribution system."74 Under such a protocol, some public utilities may not have exceeded the regulatory limits for radionuclides. New EPA rules (promulgated in 2003) require individual water well entry points to the distribution system to meet the radionuclide limits.

Presently, we are expanding our investigation in collaboration with colleagues from the Birth Defect Epidemiology and Surveillance Branch Registry. The advantage of using these more recent records is tempered by the fact that Rn-222 data are not available for these recent years. While with some caveats, Ra-226 data could be ascertained from the public utility records, Rn-222 is not monitored under the Safe Drinking Water Act and thus, data are not being gathered by any regulatory agencies. New household-level data on radon would need to be generated, which is contingent upon the availability of funds and significant technical resources.

Geospatial patterns alone are not sufficient evidence that elevated levels of radioactivity in the drinking water are causally related to the cleft defect births in the same area of Harris County, Texas. Genetic and other environmental risk factors are too complex and intertwined to be disentangled simply by comparing birth defect and environmental patterns. A more rigorous analytical treatment of the subject is necessary, such as with a concurrent prospectively matched case-control study design.75 Clarification is needed whether radium and radon exposures are direct risk factors for cleft defects, or if they are sentinels for other environmental problems related to previous land uses, such as hydrocarbon extraction, pesticides, and herbicide use in the same area. To address these issues, we have begun a pilot incident case-control investigation looking for biomarkers of exposure to uranium 238 and selected organic chemicals (pesticides and herbicides).

In spite of limitations, the association that we observed between elevated concentrations of uranium decay products and elevated orofacial cleft birth anomalies in Harris County, Texas, deserves attention. This association was (a) consistent with reports elsewhere,42 (b) biologically plausible,37 (c) temporally consistent, such that potential exposure preceded birth defect manifestation (late 1980s and early 1990s), (d) consistent in terms of geospatial distribution (northwest Harris County), and (e) defect specific. Taking this into consideration, even though the risk from other agents may markedly differ geographically, it would be unwise to ignore the possible contribution of a water-conveyed factor.

Acknowledgments
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How far can you go without destroying from within what you are trying to defend from without?

—Dwight Eisenhower