HHS Public Access

Author manuscript

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Birth Defects Res A Clin Mol Teratol. 2016 January ; 106(1): 5–15. doi:10.1002/bdra.23369.

RESIDENTIAL RADON AND BIRTH DEFECTS: A POPULATION-BASED ASSESSMENT

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Abstract

BACKGROUND—Associations have been reported between maternal radiation exposure and birth defects. No such studies were found on radon. Our objective was to determine if there is an association between living in areas with higher radon levels and birth defects.

METHODS—The Texas Birth Defects Registry provided data on all birth defects from 1999–2009 from the entire state. Mean radon levels by geologic region came from the Texas Indoor Radon Survey. The association between radon and birth defects was estimated using multilevel mixed effect Poisson regression.

RESULTS—Birth defects overall were not associated with residential radon levels. Of the 100 other birth defect groups with at least 500 cases, 14 were significantly elevated in areas with high mean radon level in crude analyses, and 9 after adjustment for confounders. Cleft lip with/without cleft palate had an adjusted prevalence ratio (aPR) of 1.16 per 1 picoCurie/liter (pCi/l) increase in

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exposure to region mean radon, 95% confidence interval (CI) 1.08, 1.26. Cystic hygroma / lymphangioma had an aPR of 1.22 per 1 pCi/l increase, 95% CI 1.02, 1.46. Other associations were suggested but not as consistent: three skeletal defects, Down syndrome, other specified anomalies of the brain, and other specified anomalies of the bladder and urethra.

CONCLUSIONS—In the first study of residential radon and birth defects, we found associations with cleft lip w/wo cleft palate and cystic hygroma / lymphangioma. Other associations were suggested. The ecological nature of this study and multiple comparisons suggest that our results be interpreted with caution.

Keywords

Radon; radiation; birth defects; malformations; cleft lip; Texas

INTRODUCTION

Birth defects are the leading cause of infant mortality in the U.S. (Petrini et al. 2002), and more than 65% are of unknown origin (Bale et al. 2003). There is continuing concern over the role of environmental factors in the etiologies of these complex outcomes, and parental exposure to ionizing radiation (IR) has long been considered a potential teratogen. Some of the key studies related to exposure to IR and the risk of adverse birth outcomes grew from evaluating atomic bomb survivors in Hiroshima and Nagasaki. Overall, findings from these studies have been inconsistent. For instance, newborns exposed in utero had microcephaly and severe developmental delay (Plummer 1952). However, later offspring of atomic bomb survivors had no detectable increase in induced mutations or chromosome abnormalities (NAS/NRC 1990; Neel et al. 1990; Otake et al. 1990). These equivocal findings were largely echoed in studies of birth defects following the Chernobyl accident in April 1986 (WHO, 2006).

While other sources of parental exposure to radiation have been explored, including occupational exposures (e.g., Wiesel et al. 2011; Lim 2014a) and medical procedures (e.g., Brent 1999), to our knowledge, there have been no assessments of radon exposure and the risk of birth defects. Radon is a naturally occurring radioactive gas that is associated with several adverse outcomes, including lung cancer. It is formed from the breakdown of radium, which arises from the radioactive decay of uranium and thorium; common exposure sources include indoor air and contaminated drinking water (ATSDR 2012). Because of the public health concerns surrounding radon exposure, the Texas Indoor Radon Survey (Smith et al. 1994) was conducted to evaluate indoor residential radon in a state characterized by its diverse geography and large population. Specifically, the objectives of the survey were to estimate (1) the statewide average indoor radon concentration in homes, and (2) regional average indoor radon concentrations to identify “hot spots”. Statewide, the arithmetic mean of radon measured in homes was 1.0 picoCuries / liter (pCi/l). This was considerably lower than 4.0 pCi/l, the US Environmental Protection Agency threshold of concern. The percentage of Texas homes above that threshold was 3.6%.

To date, there have been no assessments linking information from the statewide indoor radon survey with data from population-based health surveillance programs in Texas. As we

have one of the world's largest population-based active surveillance birth defects registries, the primary objective of this study was to determine if there is an association between living in areas in Texas with higher radon levels and occurrence of birth defects, the first such study of which we are aware. A secondary methodological objective was to treat this as a pilot for public health-driven studies examining the impact of environmental factors on the entire range of birth defects in a large and heterogeneous state; because this was an initial exploration, we examined every birth defect with at least 500 cases.

METHODS

Study Population

Data on children or pregnancies affected by birth defects came from the Texas Birth Defects Registry (TBDR) at the Texas Department of State Health Services. The TBDR is an active surveillance system including cases of structural and chromosomal birth defects born to mothers residing in Texas at the time of delivery. TBDR staff review medical records in hospitals, birthing centers, and midwifery locations, and enter relevant information for cases into a web-based system where it undergoes extensive quality checks. That information includes the mother's residence at delivery. All diagnoses must be made prenatally or within one year after delivery. The TBDR includes all pregnancy outcomes regardless of gestational age: live births (96.6% of cases), spontaneous fetal deaths (1.8%), and pregnancy terminations (1.5%). Birth defects are coded using a 6-digit system (sometimes referred to as British Pediatric Association or BPA codes) based on the British Pediatric Association and World Health Organization classification of disease, as modified by the U.S. Centers for Disease Control and Prevention and the Texas Department of State Health Services.

This study included cases delivered in 1999 (the first year the registry covered all of Texas) through 2009 (the most recent year with finalized data when this study began). Live births required as denominators for calculation of rates were taken from the same years. We grouped birth defect codes on the first four digits, resulting in categories similar to International Classification of Diseases, 9th Revision (ICD-9). All categories with at least 500 cases were then included in analyses; categories with fewer cases were excluded. For each child or fetus, data on the following variables were taken from the vital record (birth certificate or fetal death certificate) or if missing there, from the medical record: maternal age (grouped into less than 20, 20–24, 25–29, 30–34, 35–39, 40 and older) and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic), and child gender (male, female). However, the certificates were the only source of data used for maternal education (less than high school, high school, greater than high school), diabetes at any time (yes/no), and smoking during pregnancy (yes/no).

Radon Data

The Texas Indoor Radon Survey (Smith et al. 1994) was a statewide survey of indoor residential radon, conducted in January through March 1991. Owner-occupied single family dwellings were selected at random and contacted using generated telephone lists. Homeowners were asked to place an activated charcoal adsorption canister in an interior room for seven days. At the end of the seven days, they were to seal the canister and quickly

mail it directly to the US Environmental Protection Agency laboratory. Radon decay products produced by radon adsorbed on the charcoal emit gamma rays which were measured by scintillation detectors.

The random allocation of radon detectors used a regional sampling plan. Survey staff examined geological and population data for Texas and grouped all counties into regions based on their potential for indoor radon. Large metropolitan areas were designated as their own regions and sampled at a lower percentage in order to ensure that rural areas would have adequate numbers in the survey. Thirteen regions were identified. All residents within a defined region had an equal chance of being chosen in the sample. Of the 4,031 canisters sent out, 2,890 (71.7%) were returned and available for the current analysis.

We had no individual level data on radon. Instead, we assigned the arithmetic mean radon for the region (as published in the survey report) to each study subject based on the county of their mother's residence at birth.

Statistical Methods

Sociodemographic characteristics were compared between all live births and cases with birth defects using a chi-square test, where each child or fetus with a birth defect (each case) was counted only once. To determine which variables (if any) were associated with radon levels, we compared the region mean radon assigned to each live birth across various strata using analysis of variance. Subjects with missing values were not included in the above statistical tests.

This study was designed as a screening approach, looking at all birth defects with sufficient cases (here operationalized as at least 500). We evaluated associations between region mean radon level (the main independent variable) and the occurrence of each birth defect (the dependent variable) using multilevel mixed effect Poisson regression models to account for variance between/within levels, with level 1 being the individual (birth defect presence/absence, covariate values) and level 2 being the 13 geographic radon regions. In the primary analyses, the association between region mean radon level and the occurrence of each birth defect was measured using the birth prevalence ratio, both crude and adjusted for maternal race/ethnicity, age, and education. Radon was considered (a) as a continuous variable, where the birth prevalence ratio is interpreted as average change in birth prevalence per 1 pCi/l increase in exposure to region mean radon (abbreviated below as "per 1 pCi/l increase"), and (b) as rough quartiles, where the ratio is interpreted as the change in birth prevalence in a particular quartile compared with the lowest. The radon quartiles were based on the distribution of live births, attempting as much as possible with 13 region measurements, to have 25% of births in each quartile. As this was an exploratory approach, we opted to evaluate exposure both as a continuous variable and categorized according to quartiles. SAS excludes any observation that is missing data on one or more variables; we used all available observations in crude and adjusted models to maximize statistical power, acknowledging that sample sizes would decrease somewhat in the latter.

We conducted supplementary analyses when a statistically significant association was found between region mean radon level and a birth defect, after adjusting for maternal race/

ethnicity, age, and education. These included analyzing the region radon – birth defect association with the following variations. (a) We added the remaining available variables to the model (smoking, diabetes). This was to check whether any of our potentially interesting associations could be explained by adding further confounders, albeit ones with low prevalence in the population leading to frequent model non-convergence in different birth defects. (b) We analyzed cases without other major birth defects (often called “isolated” cases); either a case had only one birth defect code or if other codes were present, they were for birth defects considered minor by the National Birth Defects Prevention Study (Rasmussen et al., 2003). (c) The region with the lowest arithmetic mean radon (under the detection limit of 0.5 pCi/l, thus assigned 0.25) was within the Birth Defects Registry area that historically has had issues with low birth defects ascertainment. To check that ascertainment bias wasn’t confounding the results, we excluded that region. To balance that and avoid possible overly influential high results, we also excluded the region with the highest radon mean level. Analyses were thus rerun excluding both the highest and lowest regions. Because the lowest region comprised the entire 1st quartile, the quartile analysis was omitted.

We conducted all analyses using SAS version 9.3.

RESULTS

There were 13 geographic radon regions which covered the entire state of Texas. Their arithmetic means (the data presented in the Texas Indoor Radon Survey report) ranged from 0.25 to 3.30 pCi/l. Of the 186 birth defect groups in the TBDR, 101 (including total birth defects) had at least 500 cases and were used in the current study.

With the large numbers analyzed in this study (n=172,797 cases and n=4,207,898 live births), the frequency distribution of every variable was significantly different between total cases and live births ($p < 0.0001$, Table 1). The characteristics with the largest differences in percentage distribution indicated that case mothers tended to be older and to have diabetes, and that case infants/fetuses tended to be male.

Among live births, several characteristics were associated with mean radon (data not shown). Mothers who were White non-Hispanic had a mean radon level of 0.96 pCi/l while Black non-Hispanic mothers had 0.79 pCi/l. Radon level decreased monotonically from mothers < 20 years old (0.92 pCi/l) to mothers >= 40 years old (0.86 pCi/l). Mothers with a high school education had mean radon of 0.92 pCi/l vs. mothers with less education (0.85 pCi/l). Diabetic mothers had slightly lower mean radon while smoking mothers had higher. All of those comparisons had a p value < 0.0001. Infant sex was not associated with mean radon level ($p = 0.67$).

Birth defects were first considered as a combined group in which each infant or fetus was counted only once, regardless of the number of birth defects they had. Overall birth defects were not significantly elevated in high radon areas, either in crude analyses using continuous radon level (prevalence ratio (PR) = 1.02 per 1 pCi/l increase, 95% confidence interval (CI) 0.91, 1.15), or crude analyses using quartile level (PR comparing the 4th quartile to the 1st =

1.11, 95% CI 0.82, 1.50) (data not shown). Those impressions were also true when adjusted for maternal race/ethnicity, age, or education in continuous (adjusted prevalence ratio (aPR) = 1.01, 95% CI 0.90, 1.14) or quartile analyses (4^{th} quartile aPR = 1.09, 95% CI 0.79, 1.49) (data not shown).

Of the 100 remaining birth defect groups with at least 500 cases, 14 were significantly higher in areas with high region mean radon level when examined as a continuous variable and/or when examined as quartiles in crude analyses (Table 2). After adjusting for maternal race/ethnicity, age, and education, there were nine, although some models did not converge; this was possibly due to low power. Occurrence of cleft lip with or without cleft palate increased 16% per 1 pCi/l increase (aPR = 1.16), 95% CI 1.08, 1.26). The fourth quartile compared with the first had an aPR of 1.36 (95% CI 1.04, 1.79). Three skeletal defects showed statistically significant adjusted associations: inward deformities of the feet (4^{th} quartile aPR = 1.99, 95% CI 1.33, 2.99); reduction defects of the lower limb (continuous aPR = 1.28 per 1 pCi/l increase, 95% CI 1.06, 1.54); anomalies of the spine (4^{th} quartile aPR = 2.09, 95% CI 1.30, 3.35). Down syndrome exhibited significant adjusted association both when examined as a continuous variable (aPR = 1.09 per 1 pCi/l increase, 95% CI 1.00, 1.18) or comparing the 4^{th} quartile with the 1^{st} (aPR = 1.21, 95% CI 1.01, 1.44). Other defects were observed across other organ systems, and included cystic hygroma / lymphangioma (continuous aPR = 1.22 per 1 pCi/l increase, 95% CI 1.02, 1.46), other specified anomalies of the brain (4^{th} quartile aPR = 1.96, 95% CI 1.11, 3.48), and other specified anomalies of the bladder and urethra (4^{th} quartile aPR = 1.99, 95% CI 1.20, 3.32). One birth defect, unspecified anomalies of the heart, had lower prevalence in high radon areas, but this was not statistically significant after adjustment.

Besides Down syndrome, other chromosomal disorders such as Edwards syndrome/Trisomy 18 did not show any statistically significant associations with radon. That was also true of cardiovascular defects which made up 19 of the 101 birth defects examined.

The nine birth defects with statistically significant adjusted associations with radon were analyzed in greater depth (Table 3). Fewer models converged due to adjusting for characteristics of low prevalence (diabetes, smoking) or to analyzing fewer cases (isolated cases). In general, adjusting for maternal smoking and diabetes as well as the original race/ethnicity, age, and education, changed the estimated prevalence ratios and their 95% confidence intervals very little. The largest change in prevalence ratio was for cystic hygroma; its prevalence ratio comparing the 4^{th} quartile with the 1^{st} went from 1.78 in the original analysis to 1.83 after also adjusting for smoking and diabetes. When evaluating isolated cases, the lower number of cases resulted in wider 95% CIs as expected. The estimated PR was somewhat higher in other specified anomalies of the bladder and urethra and attenuated in anomalies of the spine. After excluding the lowest and highest regions to account for possible ascertainment problems, the PRs in the continuous radon analysis were increased for all birth defects except Down syndrome.

DISCUSSION

In the first study of its kind, assessing over 4 million births, we found that maternal residence in high radon areas was associated with the prevalence of nine out of 100 birth defects after adjustment for maternal race/ethnicity, age, and education. This is notable as the average level of radon measured in Texas homes was 1.0 pCi/l, lower than 4.0, the US Environmental Protection Agency threshold of concern. The association was not seen in all birth defects combined, and there were no birth defects with a significantly lower prevalence in high radon areas.

Although no other studies were found on birth defects and radon, several defects or defect groups have been associated in the literature with parental exposure to other sources of ionizing radiation (e.g. Brent 1999; Cech et al. 2007; Dekaban 1968; Feschchenko et al. 2002; Green et al. 2002; Plummer, 1952; Wiesel et al. 2011). Defect categories with significant associations in multiple papers (not always consistently) included chromosomal defects such as Down syndrome, central nervous system / eye, oral clefts, skeletal defects, and heart defects. Some of those were supported by findings in the current study, and many were not.

In the current study, Down syndrome occurrence was higher in high radon regions, whether radon was analyzed as a continuous variable or comparing the highest quartile vs. the lowest. However, the adjusted prevalence ratio was attenuated when excluding the lowest and highest radon regions. It was also attenuated when examining “isolated” cases, although that analysis is less appropriate for syndromes where the affected child/fetus has multiple birth defects by definition. This suggested association was consistent with reports of Down syndrome occurrence being associated with atmospheric testing of atomic weapons (Bound et al. 1995), and with chromosomal anomalies (albeit other than Down syndrome) in medical radiographers (Roman et al. 1998). It was also consistent with several reports of excess Down syndrome associated with the Chernobyl accident (Burkart et al. 1997; Sperling et al. 1994; Zatsepin et al. 2007), although those were not confirmed in other European studies (Dolk and Nichols 1999; Little 1993; WHO 2006). Chromosome abnormalities were not found among offspring of atomic bomb survivors (NAS/NRC 1990; Neel et al. 1990; Otake et al. 1990).

The literature contains many reports of central nervous system (CNS) defects, such as microcephaly (Brent 1999; Dekaban 1968; Plummer 1952), hydrocephaly (Lim et al. 2014a), Dandy Walker malformation (Lim et al. 2014b), and neural tube defects (Sever et al. 1988) in offspring of mothers exposed to radiation during pregnancy. None of these specific CNS defects were associated with high radon regions of Texas. In the current study, only ‘other specified anomalies of the brain’ showed an association with living in high radon areas; its quartile results were consistent across all analyses. It is difficult to interpret results for such categories because they are so heterogeneous. Several eye defects have been reported in association with maternal medical IR exposure (Brent 1999; Dekaban 1968; Jacobsen and Mellemgaard 1988). In our study, there were no eye defects associated with regional radon level.

In our study, cleft lip with or without cleft palate exhibited a strong and highly consistent significant association across all analyses. This is consistent with reported associations of oral clefts with tap water radioactivity (Cech et al. 2007, 2008) and with maternal treatment for Wilms tumor (Green et al. 2002).

In the current study, three skeletal defects were more prevalent in regions with higher mean radon: inward deformities of the feet (consistently significant in all analyses of quartiles), reduction defects of the lower limbs (significant with radon as a continuous variable in crude, adjusted, and fully adjusted analyses), and anomalies of the spine (not as consistently significant, such as in isolated cases). Skeletal malformations were associated with medical exposures to IR during pregnancy according to Dekeban (1968). Limb reduction defects were reported to be higher in Belarus after the Chernobyl accident (Feshchenko et al. 2002; Lazjuk et al 1997), but those studies were not supported by broader examinations (Dolk and Nichols 1999; Little 1993; WHO 2006). Feshchenko and Lazjuk also reported elevations in polydactyly, but that was not evident in our study.

The current study found a consistently strong and significant association across analyses for cystic hygroma. To our knowledge, this has not been previously reported. Other birth defect groups that exhibited associations with radon were ‘unspecified anomalies of the face and neck’ and ‘other specified anomalies of the bladder and urethra’. However, they are heterogeneous categories of birth defects and difficult to interpret.

It is notable that none of the 19 cardiovascular birth defect categories examined in our study showed a statistically significant association with residence in high radon areas. That was not consistent with reports from Jacobsen and Mellemgaard (1988), Green et al. (2002), or Lim et al (2014b). On the other hand, the lack of an association with total birth defects was consistent with the study that is probably most similar to ours in design, that of residence in high-level natural radiation areas in India (Jaikrishan et al., 1999).

Exposure to IR, especially at high doses, causes birth defects in animal models. Preconception exposure causes point mutations or chromosomal effects in offspring (Brent 1999; Russell 1977) which may then also lead to structural anomalies, whereas postconception exposure results mainly in structural anomalies. These include exencephaly (Rugh 1965), cerebellar hypoplasia (Sawada 2013), skeletal defects such as phocomelia due to a loss of skeletal progenitors (Galloway et al. 2009), and digital defects (Wang 2001) including polydactyly due to decreased programmed cell death (Yang et al. 2013). Three potential mechanisms for IR-induced embryopathy are (a) cell death or mitotic delay beyond the recuperative capacity of the embryo or fetus, (b) inhibition of cell migration, differentiation and cell communication, and (c) interference with histogenesis by processes such as cell depletion, necrosis, calcification, or scarring (Brent 1999).

While associations of birth defects with radon thus seem biologically plausible, there are at least two alternative explanations for the observed associations. First is multiple comparisons. We examined 100 independent birth defect categories with at least 500 cases (excluding total birth defects), so one might expect roughly five to be statistically significant by chance alone. If we consider that each birth defect was looked at two ways (with radon

exposure measured as a continuous variable and as an ordinal variable), that would be 200 comparisons (although it could be argued whether they are technically independent). We observed 14 significantly higher in the crude analysis, and nine after adjustment for maternal race/ethnicity, age, and education. Hence, it is possible that multiple comparisons might explain our associations. The second alternative explanation is variability in diagnosis or case ascertainment. It is possible that regions with high radon were also those areas where certain birth defects were more likely to be diagnosed, such as areas with large teaching hospitals. However, this seems unlikely for several reasons. Areas with large teaching hospitals (e.g. Houston, Dallas/Fort Worth, San Antonio) actually had lower radon levels. The region with historically low case ascertainment (Houston) might have confounded through ascertainment bias, but excluding it in our supplementary analysis did little to alter our conclusions except for Down syndrome. Finally, several of the birth defects showing associations with radon (e.g. cleft lip, skeletal defects) tend to be uniformly diagnosed and recorded (Langlois and Scheuerle 2007, Langlois et al. 2010).

There are several limitations to consider with our study. (i) Data collection on radon occurred in the winter of 1991, while the birth outcomes came from 1999–2009. Radon production levels would be constant over that period, since as progeny it is in secular equilibrium with underground radium-226 which has a half-life of 1600 years. However, methods of housing construction (e.g., air-tightness of the home, foundation type and cracks, openings around drainage pipes, etc.) or occupant behavior (e.g. opening windows) might have changed over that time, possibly affecting measured levels. Empirically, energy efficiency and material costs have been the main source of changes in home construction in last couple of decades resulting in homes that would less likely permit removal of radon and progeny. (ii) This study is highly subject to the ecological fallacy; all residences in the same region were assigned the same mean radon level. However, residential level is mainly influenced by local geology, housing construction or age, behaviors of opening windows, and time of the year, all of which could vary within a region. The resulting nondifferential misclassification would probably have biased the observed birth prevalence ratios toward the null (Bross 1954; Copeland et al. 1977). (iii) Radon exposure was based on residence at birth. In Texas, roughly 30% of mothers move between conception (closer to when birth defects occur) and birth (Canfield et al. 2006). Thus some migration was likely, but most mothers move nearby (Lupo et al. 2010) (almost always within the same county and region), so resulting nondifferential misclassification would be minimal for our study. (iv) Eighteen percent of the births in this study were in a region whose average was below the detection limit of 0.5 pCi/l, and thus were assigned the middle value of 0.25 pCi/l. However, if most of the values were actually above or below that value, it could have biased the analyses based on radon as a continuous variable. (v) Using multi-level modeling decreased statistical power and prevented many models from converging, especially those containing multiple variables. Texas has one of the largest active surveillance birth defects registries in the world, so getting even more cases may require collaborative studies with networks such as the National Birth Defects Prevention Network or EUROCAT. (vi) The mean radiation doses measured in Texas have never been associated with birth defects in any study, except a few other potentially suspect ecological studies. Also, the specific birth defect associations that we observed, if indeed causal, should have been reported in many previous studies of

(much higher dose) radiation teratogenesis, which was not found. Given those considerations and the multiple comparisons issue, our study should be taken more as screening or hypothesis-generating than hypothesis-testing; we thus invite replication by other birth defects registries.

There were several strengths with our study. The primary one was efficiency – taking advantage of existing statewide data on both exposure (residential radon levels) and outcomes (the Texas Birth Defects Registry). Also, all birth defects with sufficient cases were examined in a single study instead of several smaller studies. This complements the idea that public health interventions typically aim at one type of exposure with the goal of preventing many or all birth defects. The radon survey was well conducted and used the latest technology at the time. The statewide registry allowed examination of very large numbers of cases. Multilevel modeling, while it decreased statistical power considerably, allowed us to deal with variability and non-independence of observations in a more appropriate manner.

CONCLUSIONS

In this study, residential radon exhibited strong and consistent associations with occurrence of cleft lip with or without cleft palate, and with cystic hygroma. Associations were suggested but not quite as consistent for Down syndrome and skeletal malformations including lower limb reduction defects and inward deformities of the feet. Residential radon level was not associated with total birth defects, microcephaly, or eye defects. Since this is the first study of radon and birth defects and may have issues with ecological fallacy and multiple comparisons, replication by other researchers would be helpful. The screening approach for examining existing environmental or demographic data with the entire spectrum of birth defects was efficient and practical.

Acknowledgments

GRANT INFORMATION

This research was supported in part by a cooperative agreement between the Birth Defects Branch of the Centers for Disease Control and Prevention (CDC) and the Texas Department of State Health Services (DSHS), #U01DD000494, as well as funding from the Title V block grant at Texas DSHS. We acknowledge the support provided by the Biostatistics/Epidemiology/Research Design (BERD) component of the Center for Clinical and Translational Sciences (CCTS) for this project. CCTS is mainly funded by the NIH Centers for Translational Science Award (UL1 TR000371) by the National Center for Advancing Translational Sciences (NCATS). This work was also partially supported by R03 DE02173901. The content is solely the responsibility of the authors and does not necessarily represent the official views of the CDC, DSHS, NIH or NCATS.

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Table 1

Comparison of the distribution of characteristics between birth defects cases and all live births, Texas 1999–2009.

Characteristic[a]	Cases n (%)	Births n (%)
Total	172797 (100.0)	4207898 (100.0)
Maternal age		
Less than 20	23286 (13.5)	591973 (14.1)
20 – 24	45650 (26.4)	1177930 (28.0)
25 – 29	44638 (25.8)	1129874 (26.9)
30 – 34	35105 (20.3)	844454 (20.1)
35 – 39	18919 (11.0)	383230 (9.1)
Greater than or equal to 40	5199 (3.0)	80030 (1.9)
Missing	0	407
Maternal race/ethnicity		
White non-Hispanic	66374 (39.8)	1524191 (37.7)
Black non-Hispanic	18514 (11.1)	470448 (11.7)
Hispanic	81925 (49.1)	2045202 (50.6)
Other or Missing	5984	168057
Maternal education		
Less than high school	50384 (30.0)	1290843 (31.0)
High school	49410 (29.5)	1221193 (29.3)
Greater than high school	67929 (40.5)	1655913 (39.7)
Missing	5074	39949
Indication of Maternal Diabetes		
Yes	8684 (5.1)	148869 (3.5)
No	160745 (94.9)	4059027 (96.5)
Missing	3368	2
Maternal smoking		
Yes	10362 (6.1)	247918 (5.9)
No	158522 (93.9)	3941710 (94.1)
Missing	3913	18270
Infant sex		
Male	101503 (59.0)	2150717 (51.1)
Female	70583 (41.0)	2057181 (48.9)
Missing	711	0

[a] Frequency distribution of all covariates significantly different between cases and births at $p < 0.0001$.

Table 2

Birth defects showing potentially interesting[a] associations with region mean radon, Texas 1999–2009.

			CRUDE		ADJUSTED[b]	
Birth Defect			**# Cases**	**Prev Ratio (95% CI)[c]**	**# Cases**	**Prev Ratio (95% CI)**
Cystic hygroma, lymphangioma any site	Continuous		1104	1.24 (1.03, 1.49)	682	1.22 (1.02, 1.46)
	Quartiles:	1	116	1.00 (referent)	79	1.00 (referent)
		2	261	1.50 (0.99, 2.26)	155	1.23 (0.79. 1.92)
		3	439	1.89 (1.23, 2.89)	255	1.57 (0.97, 2.55)
		4	288	1.99 (1.32, 3.01)	193	1.83 (1.15, 2.91)
Reduction deformities of the brain	Continuous		2969	1.12 (0.95, 1.32)	2770	1.09 (0.89, 1.32)
	Quartiles:	1	339	1.00 (referent)	306	1.00 (referent)
		2	691	1.35 (1.01, 1.82)	648	n/a[d]
		3	1203	1.73 (1.29, 2.33)	1125	n/a
		4	736	1.70 (1.27, 2.28)	691	n/a
Other specified anomalies of the brain	Continuous		5292	1.22 (0.94, 1.57)	4971	1.23 (0.96, 1.58)
	Quartiles:	1	519	1.00 (referent)	475	1.00 (referent)
		2	995	1.26 (0.67, 2.36)	949	1.26 (0.69, 2.29)
		3	2515	2.16 (1.15, 4.05)	2350	2.13 (1.17, 3.89)
		4	1263	1.92 (1.06, 3.50)	1197	1.96 (1.11, 3.48)
Unspecified anomalies of the face and neck	Continuous		3903	1.08 (0.94, 1.24)	3600	n/a
	Quartiles:	1	514	1.00 (referent)	474	1.00 (referent)
		2	928	1.22 (0.93, 1.59)	863	1.25 (0.97, 1.62)
		3	1517	1.45 (1.10, 1.90)	1388	1.53 (1.17, 2.01)
		4	944	1.50 (1.15, 1.96)	875	1.50 (1.17, 1.94)
Unspecified anomalies of the heart	Continuous		1717	0.88 (0.78, 1.00)	1610	0.90 (0.79, 1.03)
	Quartiles:	1	371	1.00 (referent)	347	1.00 (referent)
		2	444	0.81 (0.58, 1.13)	423	n/a
		3	572	0.76 (0.53, 1.10)	524	n/a
		4	330	0.73 (0.53, 1.00)	316	n/a
Cleft lip with/without cleft palate	Continuous		4535	1.18 (1.09, 1.27)	4139	1.16 (1.08, 1.26)
	Quartiles:	1	652	1.00 (referent)	588	1.00 (referent)

Birth Defect			CRUDE # Cases	CRUDE Prev Ratio (95% CI)[c]	ADJUSTED[b] # Cases	ADJUSTED[b] Prev Ratio (95% CI)
		2	1080	1.15 (0.85, 1.54)	987	1.08 (0.82, 1.43)
		3	1691	1.33 (0.99, 1.80)	1543	1.30 (0.98, 1.72)
		4	1112	1.45 (1.08, 1.93)	1021	1.36 (1.04, 1.79)
Other specified anomalies of the bladder and urethra	Continuous		1058	1.21 (0.97, 1.52)	972	1.23 (0.99, 1.53)
	Quartiles:	1	115	1.00 (referent)	103	1.00 (referent)
		2	217	1.33 (0.79, 2.24)	204	1.35 (0.81, 2.26)
		3	425	1.85 (1.09, 3.13)	384	1.85 (1.10, 3.12)
		4	301	1.97 (1.17, 3.29)	281	1.99 (1.20, 3.32)
Inward (varus) deformities of the feet	Continuous		3984	1.16 (0.95, 1.41)	3739	1.17 (0.96, 1.42)
	Quartiles:	1	425	1.00 (referent)	385	1.00 (referent)
		2	874	1.45 (0.96, 2.20)	840	1.48 (0.97, 2.24)
		3	1576	1.89 (1.25, 2.86)	1459	1.90 (1.25, 2.88)
		4	1109	1.95 (1.30, 2.91)	1055	1.99 (1.33, 2.99)
Reduction defects of the upper limb	Continuous		1715	1.16 (0.98, 1.37)	1557	1.15 (0.96, 1.37)
	Quartiles:	1	197	1.00 (referent)	178	1.00 (referent)
		2	400	1.37 (1.03, 1.81)	369	n/a
		3	704	1.76 (1.33, 2.33)	632	n/a
		4	414	1.72 (1.30, 2.27)	378	n/a
Reduction defects of the lower limb	Continuous		815	1.32 (1.10, 1.58)	724	1.28 (1.06, 1.54)
	Quartiles:	1	91	1.00 (referent)	83	1.00 (referent)
		2	169	1.26 (0.24, 6.60)	152	1.20 (0.21, 6.85)
		3	343	1.88 (0.42, 8.41)	305	1.79 (0.37, 8.76)
		4	212	1.91 (0.39, 9.41)	184	1.80 (0.33, 9.82)
Other anomalies of the upper limb, including the shoulder girdle	Continuous		2650	1.07 (0.85, 1.33)	2426	1.06 (0.85, 1.33)
	Quartiles:	1	281	1.00 (referent)	258	1.00 (referent)
		2	627	1.47 (0.91, 2.39)	580	1.45 (0.87, 2.42)
		3	1108	1.95 (1.20, 3.18)	1000	1.94 (1.16, 3.25)
		4	634	1.65 (1.03, 2.66)	588	1.61 (0.97, 2.65)
Anomalies of the spine	Continuous		2307	1.17 (0.93, 1.46)	2163	n/a
	Quartiles:	1	233	1.00 (referent)	213	1.00 (referent)

Birth Defect			CRUDE # Cases	CRUDE Prev Ratio (95% CI)[c]	ADJUSTED[b] # Cases	ADJUSTED[b] Prev Ratio (95% CI)
		2	551	1.53 (0.96, 2.43)	523	1.58 (0.97, 2.57)
		3	922	2.04 (1.28, 3.25)	848	2.11 (1.30, 3.44)
		4	601	2.02 (1.28, 3.18)	579	2.09 (1.30, 3.35)
Other anomalies of the ribs and sternum	Continuous		1757	1.10 (0.80, 1.50)	1641	1.12 (0.81, 1.54)
	Quartiles:	1	148	1.00 (referent)	136	1.00 (referent)
		2	424	1.86 (0.91, 3.78)	403	n/a
		3	647	2.25 (1.10, 4.59)	595	n/a
		4	538	2.38 (1.20, 4.73)	507	n/a
Gastroschisis	Continuous		2076	1.13 (1.00, 1.27)	1923	1.05 (0.91, 1.20)
	Quartiles:	1	272	1.00 (referent)	244	1.00 (referent)
		2	532	1.32 (1.05, 1.67)	501	n/a
		3	754	1.39 (1.09, 1.76)	693	n/a
		4	518	1.56 (1.24, 1.97)	485	n/a
Down syndrome	Continuous		5506	1.02 (0.92, 1.15)	5005	1.09 (1.00, 1.18)
	Quartiles:	1	848	1.00 (referent)	759	1.00 (referent)
		2	1324	1.03 (0.77, 1.38)	1245	1.18 (0.98, 1.41)
		3	2103	1.21 (0.90, 1.62)	1870	1.34 (1.10, 1.64)
		4	1231	1.17 (0.88, 1.56)	1131	1.21 (1.01, 1.44)
Anomalies of other endocrine glands	Continuous		525	1.25 (0.91, 1.70)	476	1.27 (0.90, 1.79)
	Quartiles:	1	52	1.00 (referent)	43	1.00 (referent)
		2	99	1.30 (0.75, 2.24)	91	n/a
		3	237	2.27 (1.24, 4.16)	214	n/a
		4	137	2.13 (1.20, 3.75)	128	n/a

a. "Potentially interesting" operationally defined as a statistically significant association with region mean radon (a) treated as a continuous variable or (b) comparing the fourth quartile with the first (referent) in either crude or adjusted analyses.

b. All birth defects adjusted for maternal race/ethnicity, age, and education.

c. 95% confidence interval around the prevalence ratio.

d. n/a = Estimate not available, usually because the model did not converge.

Table 3

Supplementary analyses of birth defects showing potentially interesting[a] adjusted associations with region mean radon, Texas 1999–2009.

Birth Defect			ADJUSTING ALSO FOR SMOKING & DIABETES[b] PR (95% CI)[e]	ANALYZING ISOLATED CASES ONLY[c] PR (95% CI)	EXCLUDING LOWEST & HIGHEST REGIONS[d] PR (95% CI)
Cystic hygroma, lymphangioma any site	Continuous		1.23 (1.02, 1.47)	1.21 (1.01, 1.44)	1.54 (0.96, 2.48)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	1.22 (0.74, 2.01)	1.16 (0.11, 12.41)	
		3	1.55 (0.91, 2.65)	1.37 (0.15, 12.76)	
		4	1.78 (1.07, 2.96)	1.62 (0.16, 16.50)	
Other specified anomalies of the brain	Continuous		1.23 (0.96, 1.58)	1.35 (0.99, 1.85)	1.52 (0.97, 2.39)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	1.25 (0.68, 2.29)	1.08 (0.46, 2.58)	
		3	2.12 (1.16, 3.87)	2.16 (0.91, 5.13)	
		4	1.96 (1.10, 3.50)	2.04 (0.89, 4.66)	
Unspecified anomalies of the face and neck	Continuous		n/a[f]	1.08 (0.87, 1.34)	1.39 (1.11, 1.74)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	n/a	n/a	
		3	n/a	n/a	
		4	n/a	n/a	
Cleft lip with/without cleft palate	Continuous		n/a	1.16 (1.04, 1.29)	1.32 (1.06, 1.63)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	1.08 (0.82, 1.42)	n/a	
		3	1.30 (0.98, 1.71)	n/a	
		4	1.36 (1.04, 1.78)	n/a	
Other specified anomalies of the bladder and urethra	Continuous		1.23 (0.99, 1.53)	1.56 (1.07, 2.27)	1.84 (1.19, 2.83)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	1.36 (0.80, 2.31)	1.15 (0.26, 5.01)	
		3	1.86 (1.09, 3.19)	2.06 (0.45, 9.46)	
		4	1.99 (1.18, 3.36)	2.38 (0.56, 10.18)	
Inward (varus) deformities of the feet	Continuous		1.17 (0.96, 1.42)	1.20 (0.99, 1.44)	1.43 (1.02, 2.01)

Birth Defect			ADJUSTING ALSO FOR SMOKING & DIABETES[b] PR (95% CI)[e]	ANALYZING ISOLATED CASES ONLY[c] PR (95% CI)	EXCLUDING LOWEST & HIGHEST REGIONS[d] PR (95% CI)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	1.48 (0.97, 2.24)	1.49 (0.93, 2.40)	
		3	1.91 (1.25, 2.90)	1.80 (1.12, 2.89)	
		4	1.99 (1.33, 2.99)	1.93 (1.22, 3.07)	
Reduction defects of the lower limb	Continuous		1.28 (1.06, 1.54)	n/a	1.81 (0.26, 12.81)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	1.18 (0.21, 6.79)	n/a	
		3	1.78 (0.36, 8.73)	n/a	
		4	1.78 (0.32, 9.80)	n/a	
Anomalies of the spine	Continuous		n/a	0.99 (0.68, 1.43)	1.45 (0.96, 2.19)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	1.61 (1.04, 2.50)	1.27 (0.22, 7.41)	
		3	2.16 (1.39, 3.37)	1.59 (0.24, 10.45)	
		4	2.11 (1.37, 3.25)	1.32 (0.25, 6.95)	
Down syndrome	Continuous		n/a	1.05 (0.85, 1.30)	1.04 (0.83, 1.30)
	Quartiles:	1	1.00 (referent)	1.00 (referent)	
		2	n/a	1.29 (0.67, 2.48)	
		3	n/a	1.13 (0.59, 2.19)	
		4	n/a	1.35 (0.71, 2.56)	

a. "Potentially interesting" operationally defined as a statistically significant association with region mean radon (a) treated as a continuous variable or (b) comparing the fourth quartile with the first (referent) after adjustment for maternal race/ethnicity, age, and education (from the previous table).

b. Therefore, total covariates adjusted for include maternal race/ethnicity, age, education, smoking, and diabetes.

c. Each case has only one major birth defect; if other defects are listed, they are minor only (see text for more detailed definition).

d. Because the region with the lowest mean radon comprised the entire 1st quartile and was excluded, analysis of quartiles is not reported.

e. Prevalence ratio and its 95% confidence interval.

f. Estimate not available, usually because the model did not converge.