Risks of childhood cancer among Texas watersheds, based on mothers' living locations at the time of birth

James A. Thompson, Susan E. Carozza, Wesley T. Bissett and Li Zhu

ABSTRACT

Cancer is the most common fatal disease among US children. The fetus has reduced resistance to toxic injury and is especially prone to mutagenic injury because of the high rate of cell division. A fetus can be exposed to environmental toxins through maternal consumption of contaminated water. The objective of this study was to estimate the incidence risk for childhood cancers within each watershed in Texas. The approach modeled risk for 19 cancer histotypes incorporating correlations among the cancer types and spatial correlation. Several watersheds in a very large area known as the Central Great Plains of North Texas were associated with increased risk for astrocytoma. Two watersheds near Houston, Buffalo–San Jacinto and West Galveston Bay, had increased risk for renal cancer and acute lymphoid leukemia, respectively. A watershed in South Texas, the South Laguna Madre, had increased risk for atypical leukemias. The possibility that waterborne toxins cause these childhood cancers should be investigated further.

Key words | childhood cancer, model, multivariate, spatial, watersheds

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INTRODUCTION

Although rare in terms of absolute numbers, cancer is the most common fatal disease among US children (Pallapies 2006; Buka *et al.* 2007; Wigle *et al.* 2007). The fetus has reduced resistance to toxic injury and is especially prone to mutagenic injury because of the high rate of cell division (Anderson 2006). A fetus can be exposed to environmental toxins through maternal consumption of contaminated water. Nonpoint source (NPS) pollution is considered the major cause of water problems (Gang *et al.* 2006). NPS pollution is caused by rainfall or snowmelt moving over and through the ground in the patterns of land known as watersheds. The moving water picks up pollutants and carries them through the watershed, depositing them in streams, rivers, lakes, estuaries and into underground sources of drinking water. Sources of nonpoint pollution include both agricultural and residential pesticides, toxic chemicals from urban runoff, heavy metals and acids from abandoned mines, and atmospheric deposition. The extent to which spatial patterns of toxin-induced disease, in general, and childhood cancer, specifically, are associated with spatial patterns of water contamination should be evaluated (Thorpe & Shirmohammadi 2005).

The methods for evaluating linkage between geographic exposures and geographic risks have advanced in recent years. Geographical modeling of cancer has been important for elucidating cancer causes, and particularly for providing a geographic focus for investigation when the etiology has a spatial pattern (Lawson *et al.* 1999). When a geographic focus is being investigated, the risk factor under investigation is often a living location. When the living location and the disease outcome are both known at the individual level, the risk estimate would apply to the individual level and the estimate should be free of ecological bias (Morgenstern 2008). Thus, in addition to the objective of focusing further investigation, people can use geographic risk estimates to evaluate risks associated with their choices of living location. Unfortunately, geographic modeling of rare diseases like childhood cancer has been hampered

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by imprecise risk estimates. When a rare disease is being mapped, the crude standardized morbidity ratio (SMR), defined as the ratio of observed cases/expected cases, often has extreme values for specific locations. These extreme rates are usually characterized by very low precision.

Hierarchical and spatial approaches have been proposed to allow adjustment of risk estimates based on the extent of correlation among neighboring locations. When performed with vague priors, in a Bayesian approach, the data likelihood will determine the extent of this pooling of risks among spatial neighbors. Bayesian estimation methods have become well established among hierarchical disease mapping applications (Best *et al.* 2005). This emergence has been largely attributed to advances in computer hardware that have enabled Markov chain Monte Carlo (MCMC) implementations of relatively complex Bayesian models (Banerjee *et al.* 2004) and recently developed software that has made these techniques readily available to health researchers (Spiegelhalter *et al.* 2003). The Bayesian implementation of the Multivariate Conditional Autoregressive model provides a flexible approach to the spatial modeling of multiple childhood cancer histotypes (Thompson *et al.* 2007, 2008).

To date, geographical investigations of childhood cancer risk have concentrated on geopolitical boundaries or buffers around point sources, and have reported inconsistent results (Schreinemachers 2000; Reynolds *et al.* 2002, 2005*a*,*b*). More direct exposure assessment is needed and should be focused on areas of higher risk. Once high-risk locations like specific watersheds are identified, prospective studies will become feasible. The objective of this study was to estimate the risk of cancer to a child when the mother's living location at the time of birth was located within specific watersheds.

MATERIALS AND METHODS

A database was created to evaluate the geographic risks according to the mother's living location at the time of childbirth as determined from birth certificate data. Briefly, the creation of the database involved the retrieval of all Texas birth records from January 1, 1990 to December 31, 2002 from the Texas Department of State Health Services (TDSHS). Geocoding was performed by the TDSHS, based on street addresses, and was 87% complete. All births were followed for cancer incidence as reported to the Texas Cancer Registry (TCR) as of January 1, 2003. Therefore, a birth occurring on January 1, 1990 had 13 years of follow-up and a birth on January 1, 2002 had 1 year of follow-up. The cancer cases born in Texas were linked to the birth records using deterministic matching by birth date and sex, and probabilistic matching for names, which allowed for minor spelling variations and homonyms. The TCR is an active member of the North American Association of Central Cancer Registries (NAACCR) and follows the quality control guidelines and standards established by NAACCR (details available at the NAACCR website: http://www.naaccr.org). The TCR estimates that cancer incidence data for the state are approximately 95% complete.

Cancer diagnoses were grouped into 19 groups based on the most recent International Classification of Childhood Cancers (ICCC-3) (Steliarova-Foucher *et al.* 2005). Some pooling of very rare cancer types was performed as follows: childhood cancer subgroups Ic, Id and Ie were pooled and assigned the name "atypical leukemias"; subgroups IIb, IIc, IId and IIe were pooled into a single group and were labeled "non-Hodgkins lymphoma"; subtypes IIIe, and IIIf were pooled into a group called "atypical CNS tumors".

Statistical modeling

The hierarchical modeling approach followed a general framework. The observed counts Y_{ki} of childhood cancer histotype k in watershed i were assumed to follow independent Poisson distributions conditional on an unknown mean $E_{ki}\exp(u_{ki})$:

$$Y_{ki}|u_{ki} \sim \text{Poisson}(E_{ki}\exp(u_{ki}))$$

The expected count for histotype k in watershed i, (E_{ki}), was obtained by internal standardization from the given dataset such that the sum of observed cases for each histotype was equal to the sum of expected cases for each histotype accounting for race/ethnicity. The racial risks were estimated and compared based on the four categories of race provided by TDSHS: non-Hispanic white, Hispanic, non-Hispanic black and other. Hence $\exp(u_{kij})$ is the

standardized morbidity ratio (SMR). Watersheds with $\exp(u_{ki}) > 1$ had a greater number of observed cancer cases than expected, and vice versa for watersheds with $\exp(u_{ki}) < 1$. The log SMR u_{ki} was modeled linearly for $k = 1, \ldots, 19$ and $i = 1, \ldots, 208$ as

$$u_{ki} = \alpha_k + S_{ki}$$

with α_k being the histotype-specific intercept term representing the baseline log SMR across all watersheds and S_{ki} is the watershed- and histotype-specific log SMR. The (19×208)-dimensional matrix $\boldsymbol{S}$ was assigned a Multivariate Intrinsic Conditionally Autoregressive (MCAR) prior distribution with covariance matrix prior an inverse Wishart ($\boldsymbol{h}$,$\boldsymbol{R}$) distribution with degrees of freedom $\boldsymbol{h} = 19$ and $\boldsymbol{R}$ a 19×19 identity matrix (Thompson *et al.* 2007).

All modeling employed Bayesian inference, with vague or flexible prior beliefs and an MCMC implementation. The MCMC implementation was performed by use of WinBUGS version 1.43 (Spiegelhalter *et al.* 2003) and GeoBUGS version 1.2 (Thomas *et al.* 2003). The initial 5,000 iterations were discarded to allow for convergence and every hundred of the following 100,000 iterations were sampled for the posterior distribution. The Bayesian estimate was taken as the posterior median of the parameter and a 95% credible set was obtained from the posterior distribution quantiles. Observing convergence of two chains with widely different initial values for the random-effects precision parameters checked convergence to the posterior distribution.

The parameterization used for GIS evaluation was the posterior probability that the SMR estimate was greater than 1 (Richardson *et al.* 2004). This parameter is affected by both the magnitude and the precision of the SMR and was chosen to facilitate the objective of focusing further research on high-risk location and histotype combinations. The approach of establishing the probability of an increased risk is generally considered the first step for investigating a possible cluster and, thus, was chosen for the objective of identifying the locations with the highest likelihood of elevated risk for further geographically focused studies.

Geographical information system (GIS)

Identification of the watersheds in which mothers were living at the time of giving birth was performed by GIS analysis. Living locations, derived from the birth database, were plotted and located within watersheds with watershed boundaries provided by ArcView® GIS 3.2 (Environmental Systems Research Institute, Inc., Redlands, CA). Known water hazards were also added to the GIS analysis. Known water hazards included the Environmental Protection Agency (EPA) list of regulated release sites and the National Priority List of superfund sites. Maps of the aquifers of Texas were retrieved from the Texas Commission on Environmental Quality (TCEQ) website (http://www.tceq.state.tx.us/gis/index.html).

RESULTS AND DISCUSSION

The objective of this study was to evaluate the risks of childhood cancer associated with maternal residence at birth within specific Texas watersheds. Linkage of the cancer and birth databases identified 3718 cancer cases distributed among 19 histotype groups and 3,805,745 total births. The frequency of each histotype is given in Table 1. In order to identify high-risk locations, the current study used the posterior likelihood of a relative risk greater than 1 (Richardson *et al.* 2004). A total of nine Texas watersheds had higher than 90% posterior likelihood of an SMR greater than 1 for a childhood cancer histotype (Table 2). The locations of the watersheds are shown in Figure 1.

Bayesian hierarchical modeling automatically accounts for what frequentists refer to as the multiple comparison problem. With a frequentist analysis, there is a possibility of finding large differences as a result of searching through a large number of possibilities. The current study estimated the relative risk for 19 cancers in each of 208 watersheds. The Bayesian approach that was used provides an adjustment of extreme rates, or what is often known as a "shrinkage to the mean." In the current study this adjustment included an adjustment toward the overall intercept, a second adjustment toward the spatial expectation as determined by the rates in the neighboring watersheds and a third adjustment toward mean rate of the 19 cancers within the watershed. In Bayesian hierarchical modeling, the amount of the adjustment or shrinkage is greatest when the expected rates of disease are low. Expected

Table 1 | Classification and frequencies of childhood cancer histotypes. Cancer histotype groups were grouped by International Classification of Childhood Cancers—3. A common name for the histotype classification is listed along with the frequency counts and percents

ICCC3 group	Common name for histotype group	*n*	%
Ia	Acute lymphoid leukemias (ALL)	968	26.0
Ib	Acute myeloid leukemias (AML)	180	4.8
Ic,d,e	Atypical leukemias	100	2.7
IIa	Hodgkin lymphoma	55	1.5
IIb,c,d,e	Non-Hodgkins lymphoma	194	5.2
IIIa	Ependymoma and choroid plexus tumor	100	2.7
IIIb	Astrocytomas	322	8.7
IIIc	Intracranial and intraspinal embryonal tumors	176	4.7
IIId	Other gliomas	120	3.2
IIIe,f	Atypical CNS tumors	161	4.3
IV	Neuroblastoma and other peripheral nervous cell tumors	374	10.1
V	Retinoblastoma	179	4.8
VI	Renal tumors	268	7.2
VII	Hepatic tumors	82	2.2
VIII	Malignant bone tumors	53	1.4
IX	Soft tissue and other extraosseous sarcomas	259	7.0
X	Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	127	3.4
XI	Other malignant epithelial neoplasms and malignant melanomas	60	1.6
XII	Other and unspecified malignant neoplasms (including uncoded)	37	1.0

disease rates are low when there is only a small population at risk, which in the current study would be the watersheds with low birth rates. The shrinkage is also greater for rare diseases such as childhood cancer.

A contiguous collection of watersheds in the Great Plains in North Texas (Lake Meredith, Upper Prairie Dog Town Fork Red, Middle Canadian-Spring, Upper North Fork Red, Upper Salt Fork Red and Middle North Fork Red) had high posterior likelihoods for increased risk of astrocytomas. The area of high risk was very large with very high statistical likelihood for an elevated risk. Geographical Information System analysis showed that these watersheds were largely overlying the Ogallala aquifer. These watersheds also had 120 EPA-regulated sites including a single superfund site (Figure 2). There are at least two suspected potential toxic exposures spread through the water in this location: pesticide applications in this largely agricultural area and drinking water contamination from the Federal superfund site.

Pesticide exposure has long been postulated as a cause of childhood cancer and has been the focus of many studies: however, an unambiguous mechanistic cause-and-effect relationship has not been demonstrated (Infante-Rivard & Weichenthal 2007). Some studies whose objectives were to evaluate pesticide exposure as a risk factor for childhood cancers provide support for farm or rural living as a risk factor (Nasterlack 2007). Rural communities are different from urban communities in a great many ways, including quality of drinking water. Water quality has often been evaluated by pesticide content but pesticides are probably markers for total agronomy activity in combination with soil and water conditions. Widespread contamination of surface water and rural/urban differences has been shown in three of Texas' water systems, including the Central High Plains Aquifer, the Trinity River Basin and the South Central Texas Watershed (Land *et al.* 1998; Bush *et al.* 2000; Becker *et al.* 2002). Nearly all water samples contained pesticides. The Ogallala aquifer is known to have high levels of arsenic, thought to be derived from agricultural pesticide applications, but some consider local rock formations as some of the arsenic source (Hudak 2000; Reedy *et al.* 2007). Inorganic arsenic exposure through drinking water is associated with cancers in adults; however, the carcinogenic potential in children remains unknown (Moore *et al.* 2002).

Near the center of the elevated risk for astrocytomas is a Federal superfund site known as the Pantex Plant. The plant began in 1942 as an Army Ordnance Corps facility and continues as an active facility performing fabrication, testing and disassembly of nuclear weapons. The plant has had discharges into the large Ogallala aquifer underlying the six watersheds in the high-risk area. The ground water pumped from the Ogallala Aquifer provides drinking water to the city of Amarillo and the surrounding area. Testing has identified explosives, trichloroethylene, 1,2-dicholoroethane, chromium and perchlorate in the Ogallala aquifer. Pumping of the city water wells has created a cone of

Table 2 | Watershed–histotype combinations with high SMR

		SMR risk percentiles			
	Cancer	**2.5**	**50**	**97.5**	**Posterior probability that SMR >1**
Lake Meredith	Astrocytoma	0.94	1.52	2.73	0.95
Upper Prairie Dog Town Fork Red	Astrocytoma	0.94	1.54	2.67	0.95
Middle Canadian-Spring	Astrocytoma	0.83	1.46	3.30	0.91
Upper North Fork Red (BUGS # 17)	Astrocytoma	0.91	1.54	2.85	0.94
Upper Salt Fork Red	Astrocytoma	0.81	1.46	2.88	0.90
Middle North Fork Red	Astrocytoma	0.77	1.50	3.36	0.90
Buffalo–San Jacinto	Renal	1.00	1.31	1.73	0.97
West Galveston Bay	ALL	0.95	1.23	1.62	0.94
South Laguna Madre	Atypical leukemia	0.92	1.54	2.58	0.96

depression, causing ground water in the Ogallala underlying Pantex to flow toward the city well field (EPA 2008).

The excess incidence of astrocytomas in this area constitutes a very large geographic area and the risk was estimated with relatively high statistical certainty. Further study should include disease mapping with a more continuous risk surface. This could be performed using individual geocoordinates or by pixilating a surface into smaller areal units. This may provide insight into the relative likelihoods of a point source water contamination by a Federal superfund site versus a broad common exposure of agricultural pesticides.

Two watersheds near Houston (Buffalo–San Jacinto and West Galveston Bay) had increased risk for renal

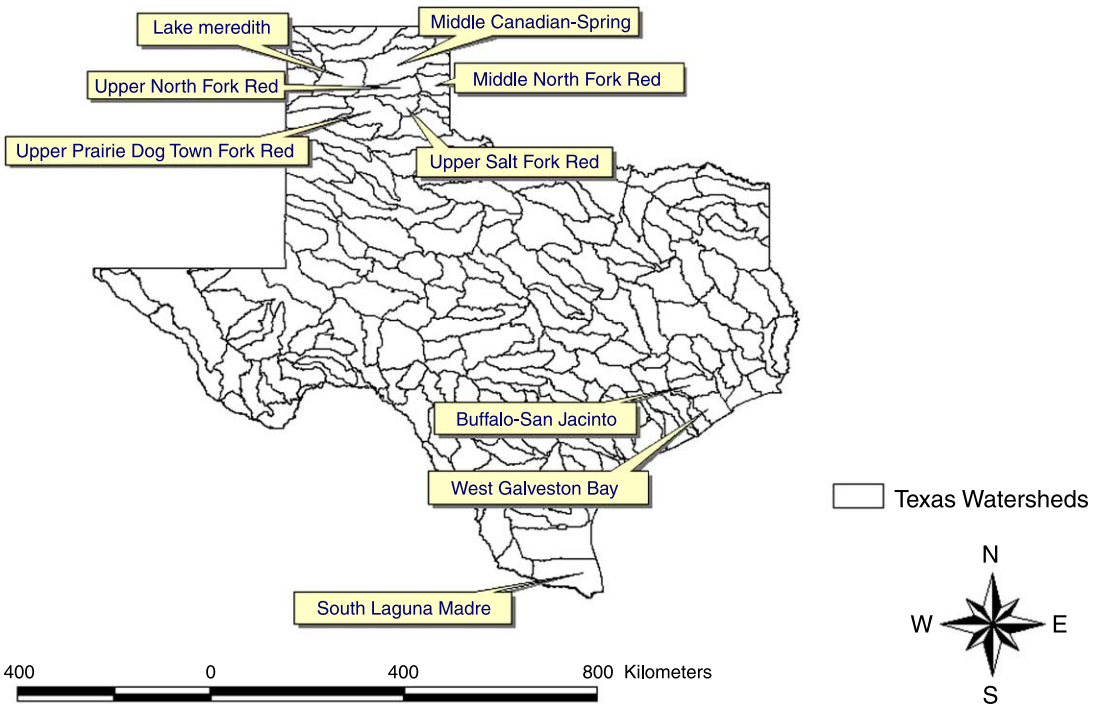

Figure 1 | Location of watersheds with high posterior probability of elevated (>1) Standard Morbidity Ratios for childhood cancer.

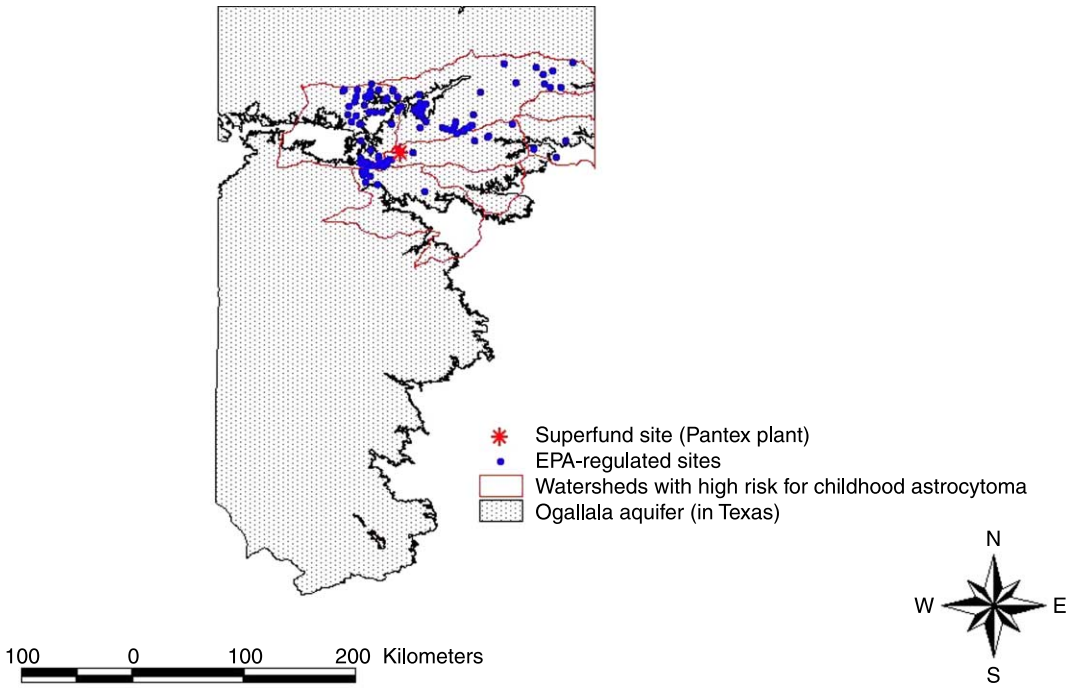

Figure 2 | Known water hazards in the location of high risk for astrocytomas.

cancer and acute lymphoid leukemia, respectively. Wilms tumor is the most common of the renal tumors. Wilms tumors and other renal tumors have peak incidence very early in infancy, suggesting a fetal exposure, but very little is known about the etiology. Acute lymphoid leukemia (ALL) is the most common and most studied childhood cancer. Recent evidence has implicated fetal exposures, and cytogenetic changes in neonatal blood

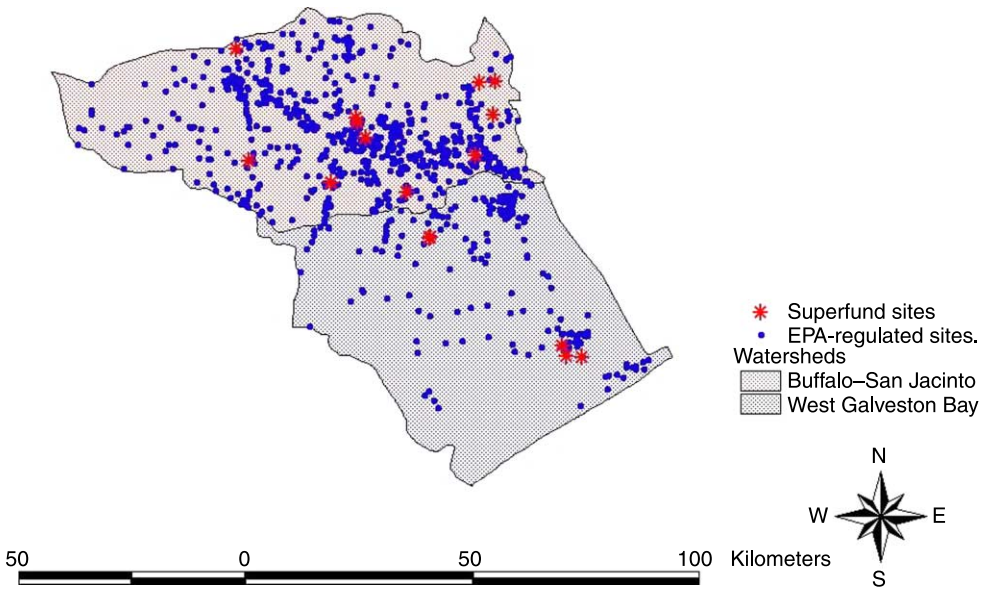

Figure 3 | Known water hazards in the location of high risk for childhood cancer in two watersheds near Houston, including renal cancer in the Buffalo–San Jacinto watershed and acute lymphoid leukemia in the West Galveston Bay watershed.

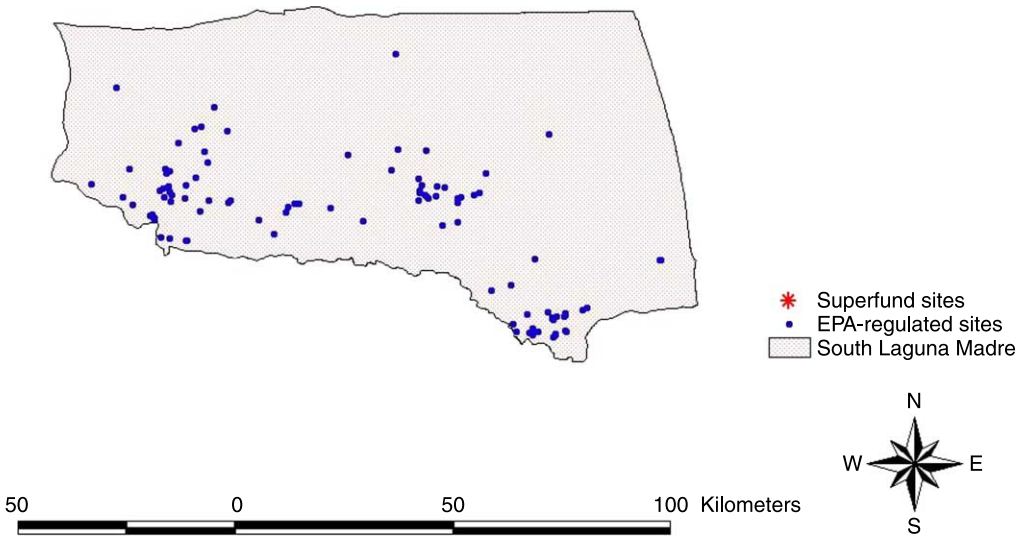

Figure 4 | Known water hazards in the South Laguna Madre watershed, found to have a high risk for atypical leukemias.

have been demonstrated. ALL has been linked to benzene and other solvent contamination of drinking water (Ries *et al.* 1999; Mcnally & Parker 2006). ALL has a prominent incidence in early infancy for white children but not for black children, suggesting that the role of prenatal exposures or genetic resistance may be different among these race groups. These two watersheds, near Houston, had 986 EPA-regulated sites including 15 superfund sites (Figure 3). Fuller investigation could include a more detailed risk surface as it is likely that some areas within the watershed have higher and lower risk likelihoods. Also, spatial epidemiologists value the evidence of a risk gradient. For example, if a toxic air-release causes a health problem there should be a gradient of risk away from the source. Studies would provide superior causal evidence if the results included a map of risk that demonstrated a risk gradient away from the suspect source. Multiple point sources should demonstrate a more complex risk surface with multiple peaks and valleys. Defining the spatial process, specifically the risk-surface around point sources, should be the subject of further research.

A mother's birth residence in the South Laguna Madre watershed was associated with increased risk for atypical leukemias, a diverse collection of very rare leukemias that excluded the more common leukemias, acute lymphoid leukemia and acute myeloid leukemia. These cancers are rare and little is known about the causes (Ries *et al.* 1999). This watershed had 104 EPA-regulated sites with no superfund sites (Figure 4).

CONCLUSIONS

Nine watersheds in Texas were associated with a high probability of increased risk for specific types of childhood cancer. A large area involving six contiguous watersheds in the Great Plains in North Texas had an increased risk for astrocytoma. Other specific watersheds had high risk for renal cancer, acute lymphoid leukemia and atypical leukemias. Further research should address these location and cancer type combinations. Specifically, the possibility that waterborne toxins cause these childhood cancers should be investigated further.

COMPETING INTERESTS

The authors have no competing interests.

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REFERENCES

Anderson, L. M. 2006 Environmental genotoxicants/carcinogens and childhood cancer: bridgeable gaps in scientific knowledge. *Mutat. Res. Genetic Toxicol. Environ. Mutagen.* **608**(2), 136–156.

Banerjee, S., Carlin, B. P. & Gelfand, A. E. 2004 *Hierarchical Modeling and Analysis for Spatial Data*. Chapman & Hall/CRC, Boca Raton, FL.

Becker, M. F., Bruce, B. W., Pope, L. M. & Andrews, W. J. 2002 *Ground-Water Quality in the Central High Plains Aquifer, Colorado, Kansas, New Mexico, Oklahoma, and Texas, 1999*. U.S. Geological Survey Water-Resources Investigations Report, 02-4112. US Geological Survey, Denver, CO.

Best, N., Richardson, S. & Thomson, A. 2005 A comparison of Bayesian spatial models for disease mapping. *Stat. Methods Med. Res.* **14**(1), 35–59.

Buka, I., Koranteng, S. & Vargas, A. R. O. 2007 Trends in childhood cancer incidence: review of environmental linkages. *Pediatr. Clin. N. Am.* **54**(1), 177–203.

Bush, P. W., Ardis, A. F., Fahlquist, L., Ging, P. B., Hornig, C. E. & Lanning-Rush, J. 2000 *Water Quality in South-Central Texas*. U.S. Geological Survey Circular 1212. US Geological Survey, Denver, CO.

EPA 2008 Pantex Plant (USDOE). Available at: http://www.epa.gov/earth1r6/6sf/pdffiles/0604060.pdf (Last accessed: 8 January 2009).

Gang, D. C., Lee, K. Y. & Kadari, R. K. 2006 Nonpoint sources. *Water Environ. Res.* **78**(10), 1958–1974.

Hudak, P. F. 2000 Distribution and sources of arsenic in the southern High Plains Aquifer, Texas, USA. *J. Environ. Sci. Health Part A Toxic/Hazard. Subst. Environ. Eng.* **35**(6), 899–913.

Infante-Rivard, C. & Weichenthal, S. 2007 Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. *J. Toxicol. Environ. Health Part B Crit. Rev.* **10**(1–2), 81–99.

Land, L. F., Moring, J. B., Van Metre, P. C., Reutter, D. C., Mahler, B. J., Shipp, A. A. & Ulery, R. L. 1998 *Water Quality in the Trinity River Basin, Texas, 1992–95*. US Geological Survey Circular 1171. US Geological Survey, Denver, CO.

Lawson, A. B., Bohning, D., Biggeri, A., Lesaffre, E. & Viel, J.-F. 1999 Disease mapping and its uses. In *Disease Mapping and Risk Assessment for Public Health* (ed. A. Lawson, A. Biggeri, D. Bohning, E. Lesaffre, J.-F. Viel & R. Bertollini), pp. 3–13. Wiley, New York.

Mcnally, R. J. Q. & Parker, L. 2006 Environmental factors and childhood acute leukemias and lymphomas. *Leuk. Lymph.* **47**(4), 583–598.

Moore, L. E., Lu, M. & Smith, A. H. 2002 Childhood cancer incidence and arsenic exposure in drinking water in Nevada. *Arch. Environ. Health* **57**(3), 201–206.

Morgenstern, H. 2008 Ecologic studies. In *Modern Epidemiology*, 3rd edition. (ed. K. Rothman, S. Greenland & T. L. Lash), pp. 511–531. Lippincott, Williams & Williams, Philadelphia.

Nasterlack, M. 2007 Pesticides and childhood cancer: an update. *Int. J. Hyg. Environ. Health* **210**(5), 645–657.

Pallapies, D. 2006 Trends in childhood disease. *Mutat. Res. Genetic Toxicol. Environ. Mutagen.* **608**(2), 100–111.

Reedy, R. C., Scanlon, B. R., Nicot, J. P. & Tachovsky, J. A. 2007 Unsaturated zone arsenic distribution and implications for groundwater contamination. *Environ. Sci. Technol.* **41**(20), 6914–6919.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., Hertz, A. & Harnly, M. E. 2002 Childhood cancer and agricultural pesticide use: an ecologic study in California. *Environ. Health Perspect.* **110**(3), 319–324.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., Harnly, M. & Hertz, A. 2005 Agricultural pesticide use and childhood cancer in California. *Epidemiology* **16**(1), 93–100.

Reynolds, P., Von Behren, J., Gunier, R., Goldberg, D. E. & Hertz, A. 2005 Agricultural pesticides and lymphoproliferative childhood cancer in California. *Scand. J. Work Environ. Health* **31**, 46–54.

Richardson, S., Thomson, A., Best, N. & Elliott, P. 2004 Interpreting posterior relative risk estimates in disease-mapping studies. *Environ. Health Perspect.* **112**(9), 1016–1025.

Ries, L. A. G., Smith, M. A., Gurney, J. G. Linet, M., Tamra, T., Young, J. L. & Bunin, G. R (eds.) 1999 *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995*. NIH Pub. no. 99–4649, Bethesda, MD.

Schreinemachers, D. M. 2000 Cancer mortality in four northern wheat-producing states. *Environ. Health Perspect.* **108**(9), 873–881.

Spiegelhalter, D., Thomas, A., Best, N. & Lunn, D. 2003 *WinBUGS User Manual: Version 1.4*. MRC Biostatistics Unit, Cambridge.

Steliarova-Foucher, E., Stiller, C., Lacour, B. & Kaatsch, P. 2005 International classification of childhood cancer. 3rd edition. *Cancer* **103**(7), 1457–1467.

Thomas, A., Best, N. & Lunn, D. 2003 *GeoBUGS User Manual Version 1.2*. MRC Biostatistics Unit, Cambridge.

Thompson, J. A., Carozza, S. E. & Zhu, L. 2007 An evaluation of spatial and multivariate covariance among childhood cancer histotypes in Texas (United States). *Cancer Causes Control* **18**(1), 105–113.

Thompson, J. A., Carozza, S. E. & Zhu, L. 2008 Geographic risk modeling of childhood cancer relative to county-level crops, hazardous air pollutants and population density characteristics in Texas. *Environ. Health* **7**, 45.

Thorpe, N. & Shirmohammadi, A. 2005 Herbicides and nitrates in groundwater of Maryland and childhood cancers: a geographic information systems approach. *J. Environ. Sci. Health Part C Environ. Carcinogen. Ecotoxicol. Rev.* **23**(2), 261–278.

Wigle, D. T., Arbuckle, T. E., Walker, M., Wade, M. G., Liu, S. L. & Krewski, D. 2007 Environmental hazards: evidence for effects on child health. *J. Toxicol. Environ. Health Part B Crit. Rev.* **10**(1–2), 3–39.

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