

Geographic risk modeling of childhood cancer relative to county-level crops, hazardous air pollutants and population density characteristics in Texas

James A. Thompson^{1§}, Susan E. Carozza², Li Zhu²

¹Department of Large Animal Clinical Science, Texas A&M University, College Station, Texas, USA 77843-4475

²Department of Epidemiology and Biostatistics, School of Rural Public Health, Texas A&M University, College Station, Texas, USA, 77843

[§]Corresponding author

Email addresses:

JAT: jthompson@cvm.tamu.edu

SEC: scarozza@srph.tamhsc.edu

LZ: lizhu@srph.tamhsc.edu

Abstract

Background: Childhood cancer has been linked to a variety of environmental factors, including agricultural activities, industrial pollutants and population mixing, but etiologic studies have often been inconclusive or inconsistent when considering specific cancer types. More specific exposure assessments are needed. It would be helpful to optimize future studies to incorporate knowledge of high-risk locations or geographic risk patterns. The objective of this study was to evaluate potential geographic risk patterns in Texas accounting for the possibility that multiple cancers may have similar geographic risks patterns.

Methods: A spatio-temporal risk modeling approach was used, whereby 19 childhood cancer types were modeled as potentially correlated within county-years. The standard morbidity ratios were modeled as functions of intensive crop production, intensive release of hazardous air pollutants population density, and rapid population growth.

Results: There was supportive evidence for elevated risks for germ cell tumors and “other” gliomas in areas of intense cropping and for hepatic tumors in areas of intense release of hazardous air pollutants. The risk for Hodgkin lymphoma appeared to be reduced in areas of rapidly growing population.

Conclusions: The study identified cancer histotypes and county environmental conditions for further study. However, specific environmental factors were generally unrelated to childhood cancer on the county-level scale.

Background

Childhood cancer has been linked to a variety of environmental factors, including agricultural activities, industrial pollutants and population mixing. Geographical modeling of cancer has been important for elucidating cancer causes when the etiology has a spatial pattern [1]. The evidence that childhood cancer types may share common geographic patterns [2,3] heightens the importance of identifying geographic-based risks for childhood cancer.

Pesticide exposure has long been implicated 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 [4]. Some studies whose objectives were to evaluate pesticide exposure used cropping intensity as an exposure surrogate and implicated farm or rural living as a positive risk factor [5]. However, geographic investigation has concentrated on geopolitical boundaries or buffers around point sources and have lead to inconsistent results when each individual cancer type is considered among studies [6-10]. Even if an association was consistent, rural communities are different from urban communities in a great many ways, including population density characteristics and the extent of industrial pollution. Further research should be focused in high-risk areas to evaluate specific exposures and specific cancer types.

Hazardous air pollutants (HAP) have been linked to increased cancer risks for individuals living in close proximity to major point source HAP-releases. For example, childhood cancers and leukemias in Great Britain exhibited geographical clustering of birth places

close to environmental hazards that included large scale combustion processes, processes using volatile organic compounds and waste incineration [11-13]. When areal source HAP were modeled at the census tract level, modeled values were related to leukemia rates in California [14]. Automobile exhaust is an area-source HAP that has received considerable scrutiny as a potential cause of childhood cancer. The studies have shown conflicting results and a critical review concluded that the weight of the epidemiological evidence indicates no increased risk for childhood cancer associated with exposure to traffic-related residential air pollution [15]. If surrogate exposure, like proximity to releases, is related to a rare disease, like childhood cancer, then investigation should focus on the higher risk locations.

Infectious causes of childhood cancer have been proposed and population characteristics of stability or mixing have been proposed and evaluated [16]. An Ohio study examined the geographic distribution of childhood leukemias relative to population density, population growth, and rural/urban locale. The study found higher rates for acute lymphocytic leukemia among the counties with most rapid population growth and the most urbanized counties had reduced risk for acute myeloid leukemia. The authors reasoned that the findings supported population mixing as a cause of some childhood cancers [17]. Mixing at the population level must have risks that can be estimated and communicated at the individual level. The risks for an individual to move or to be exposed to movers should be parsed and estimated in a more focused study.

The three types of proposed causal factors (cropping, HAP release and population density characteristics) are especially likely to be confounded in Texas where the spatial relationships

between agricultural activity, industrial locations and characteristics of the population are especially complex. The objective of this study was to perform Bayesian geographical risk modeling of childhood cancer accounting for potential correlations among histotypes. Geographic patterns were assessed relative to county-level cropping intensity, intensive industrial releases of HAP and population density and growth. The goal of the study was to estimate the risk to an individual child based on specific characteristics of the mother's living location at the time of childbirth. Once higher risk locations are identified and characterized, more specific personal risk models can be developed.

Methods

Childhood cancer database.

All Texas birth records from January 1, 1990 to December 31, 2002 were retrieved from the Texas Department of State Health Services (TDSHS). All births were followed for cancer incidence as reported to the Texas Cancer Registry (TCR) as of January 1, 2003. Therefore, a birth occurring January 1, 1990 had 13 years of follow-up and a birth on January 1, 2002 had 1 year of follow-up. 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.naacr.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) [18]. Some pooling of very rare cancer types was performed as follows: childhood cancer subgroups Ic, Id and Ie were pooled and assigned the name "other

leukemias”; subgroups IIb, IIc, II d and IIe were pooled into a single group and were labeled “non-Hodgkin lymphoma”; and subtypes IIIe, and III f were pooled into a group called “other CNS tumors.” The database provided records for 3718 cancer cases distributed among 19 histotype groups and 3,805,745 total births.

County-level agronomy practices.

To evaluate annual crop production, data were retrieved from the Texas Almanac Characterization Tool Version 2.0.4 (Blackland Research and Extension Center, Texas Agricultural Experiment Station, Texas A&M University System, 720 East Blackland Road, Temple, TX, USA). By acreage, there are four major crops in Texas: corn, soybeans, wheat, and sorghum. When the combined total acres planted in these crops exceeded 20% of the county’s total area, the county-year was classified as extensive cropping. The definition was chosen to identify the highest production locations but also to maintain an adequate number of high production county-years for estimation stability.

County-level HAP

Hazardous air pollutants are substances that are known to be carcinogenic or to cause other serious health problems. The Environmental Protection Agency (EPA) currently identifies and records the release of 188 HAP. The data regarding Texas industries with air emissions of chemicals were available from the Toxic Release Inventory (TRI) program, a publicly available database of toxic chemical releases. This inventory was established under the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) and expanded by the Pollution Prevention Act of 1990. The EPA compiles the TRI data each year and makes it available through several data access tools, including the

TRI Explorer and Envirofacts. The data are available as either county emission summaries (county-level) or facility-specific emissions (point-source). Releases from four industries, petroleum refineries (Standard Industrial Code (SIC) Major Group 29), petroleum refining and related industries (SIC Major Group 33), chemical industries (SIC Major Group 28) and plastics production (SIC Major Group 30), were retrieved. The total releases were summed to identify high-release county-years. For year-to-year consistency, the list of 1988 core chemicals was used. A county-year in which 100,000 kg of toxic substances were released was considered to be high intensity HAP release. This definition identified the highest release county-years while maintaining enough intensive-release county-years for estimation stability.

County-level population density.

Counties were classified on population estimates from the US census bureau; the same source was used for estimates for intercensus years. County-years with populations of more than 1 million were classified as metropolitan and county-years with more than 50,000 residents were classified as urban. These are the standard definitions used by the U.S. census. County-years that showed population growth of more than 1 percent from the previous year were classified as rapid growth. The definition was chosen to be comparable to a recent study that evaluated a similar growth rate [17].

Disease Modeling

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

$$Y_{kij} \mid u_{kij} \sim \text{Poisson}(E_{kij} \exp(u_{kij}))$$

The expected count for histotype k in county i , and year j (E_{kij}) was obtained by internal standardization from the given dataset such that the sum of observed cases for each histotype was exactly equal to the sum of expected cases for each histotype accounting for race. Race was defined as the mother's race as identified as one of four classes on the birth record: white, black, Hispanic and other. Hence $\exp(u_{kij})$ is the standardized morbidity ratio (SMR). County-years with $\exp(u_{kij}) > 1$ had greater number of observed cancer cases than expected, and vice versa for counties with $\exp(u_{kij}) < 1$. The log-SMR u_{kij} was modeled linearly for $k=1, \dots, 19$ histotypes and $i=1, \dots, 254$ counties and $j=1, \dots, 13$ years, as

$$u_{kij} = \alpha_k + S_{ki} + \text{Year}_{ij} + \beta 1_k * \text{HAPS}_{ij} + \beta 2_k * \text{CROPS}_{ij} + \beta 3_k * \text{METRO}_{ij} + \beta 4_k * \text{URBAN}_{ij} + \beta 5_k * \text{GROWTH}_{ij}$$

The α_k represent the histotype-specific intercept terms for the baseline log-SMR across all counties and were assigned 19 independent flat priors. The S_{ki} represent the county and histotype-specific log-SMR due to unmeasured or random county effects. The 19×254 dimensional matrix \mathbf{S} was assigned a Multivariate Intrinsic Conditionally Autoregressive (MCAR) prior distribution with covariance matrix prior an inverse Wishart (\mathbf{h}, \mathbf{R}) distribution with degrees of freedom $\mathbf{h} = 19$ and \mathbf{R} , a 19×19 identity matrix. Year represented the risk for year of birth which contained the risk for the varying

periods of observation and was assigned 19 independent random walk priors. Indicator variables ($HAPS_{ij}$, $CROPS_{ij}$, $METRO_{ij}$, $URBAN_{ij}$ and $GROWTH_{ij}$) were derived from the data as previously described for high intensity HAP release, high crop production, metropolitan, urban, and rapid population growth county-years, respectively. The β 's represented the log-relative risk for the county characteristics and were assigned a non-informative normal prior distribution.

All modeling.

All models 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 [19] and GeoBUGS version 1.2 [20]. The initial 1,000 iterations were discarded to allow for convergence and every hundredth 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 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.

Results

Two hundred and fifty four counties were modeled for 13 years providing 3302 county-years. The majority of county-years (79.1%) were classified as rural with a population of less than 50,000. For each year of the study there were exactly 4 metropolitan counties having more than 1 million residents, Bexar, Dallas, Harris and Tarrant counties.

Population growth varied widely with population losses of more than 1% to population growth of greater than 4 % both common. Growth of greater than 1% occurred in 41.7% of the county-years (Figure 1). The amount of HAP-release was commonly less than 50 tonnes per county-year but some very high releases were recorded, with 15.8% of the county-years having greater than 100 tonnes of release (Figure 2). Most county-years had less than 10% of the county area planted in corn, sorghum, cotton and wheat; however some county-years had greater than 50%, with 20.1% of the county-years having greater than 20% of the county cropped with these four crops (Figure 3).

Year was included in the model to adjust for varying periods of years-at-risk. Children born January 1, 1990 were followed for 13 years and children born January 1, 2002 for 1 year. Independent random walk priors were used to allow autoregressive temporal smoothing for each histotype. Temporal trends were readily identifiable and they varied considerable among histotypes. Two cancers with the greatest decrease in risk over the period of study were bone tumors (e.g. osteosarcoma) and Hodgkin lymphoma. These are cancers considered most common in teenagers. Two cancers with relatively steady risk over the study period were AML and “other leukemias.” These two cancers are considered most common in very young infants. The temporal smoothing parameters used in the study are presented in Figure 4.

For the combination of 5 geographical risk indicators and 19 cancer types, there were no SMRs whose 95% credible sets were above 1. Hodgkin lymphoma appeared to be occurring with reduced risk in rapidly growing counties. There was support for an

increased risk for hepatic tumors associated with high-release HAP locations and for germ cell tumors and “other” gliomas among high crop production locations. The median SMR and the 95% credible sets are listed in Table 1.

Discussion

The investigation reported here estimated personal risks for a child to develop cancer. This risk was defined by the mother’s living location at the time of birth. There is also interest in other potential critical periods of exposure including earlier in gestation and the neonatal period. Also, it may be that many environmental exposures act not as tumor initiators, but as tumor promoters, so that exposures closer to diagnosis are also of interest. These were issues not addressed in the current study. Risk estimates were computed under a Bayesian paradigm maintaining sources of uncertainty in the risk estimates. The county-level parameters were used as potential indicators of high risk to identify high-risk locations for further study and were selected from the conflicting evidence supporting their possible role as causes of childhood cancer. Once high-risk locations and their characteristics are identified, prospective studies will become feasible. These studies could include more specific assessment of environmental exposures.

The current study was designed to evaluate patterns of geographic risk. The majority of the SMRs were very close to 1 with the strength of the study being the narrow 95% credible sets. The precision achieved in the current study was related to the incorporation of two sources of covariance, covariance among histotypes and spatial covariance. Previous epidemiologic studies have often used broad case definitions and frequently

pooled data from multiple childhood cancer histotypes. The appropriateness of this pooling is largely unknown. Pooling cancer types with disparate causes will lead to a non-differential misclassification and usually increase the likelihood of a null finding. Failure to pool cancer types with common causes will lead to an unnecessary loss of precision. Specifying a flexible prior for the covariance matrix, in a Bayesian approach, can preserve this uncertainty. Under Bayesian modeling, if two diseases are poorly correlated, the outcomes will remain relatively uncorrelated in the posterior distribution and the risk estimates will be the similar to estimates calculated independently for each histotype. Hierarchical approaches have been proposed to estimate the extent of correlation among neighboring locations to allow for appropriate adjustment of risk estimates. When performed with vague priors, in a Bayesian approach, the data likelihood will determine the extent of this pooling. The result was that the current study estimated quite narrow 95% credible sets, relative to previous studies.

The current study supports further studies on germ cell tumors and other gliomas in areas with intensive cropping. Several studies have linked georeferenced disease counts and cropping patterns as a surrogate for pesticide exposure [7-10,21]. These studies varied widely on how cropping patterns were defined as exposure and how the childhood cancers, as a group of outcomes, were pooled or parsed as outcomes. However, when risks of specific cancer types are evaluated subjectively among studies, the cumulative evidence supports the null finding. For the vast majority of childhood cancer types, the current study goes beyond a frequentist null conclusion by demonstrating SMR that were close to 1 with narrow 95% credible sets.

The current study supports the study of childhood hepatic cancer in areas of intense HAP release. The SMR for hepatic tumors was 1.87 (0.95, 3.98) for county-years with greater than 100,000 kg of HAP releases. Studies evaluating air pollution as a cause of childhood cancer have been inconsistent both among cancer types [22] and for leukemia, the most commonly studied childhood cancer [23]. Several studies have evaluated multiple cancer types and groupings and found one or more histotypes at increased risk but other studies have found other histotypes at risk. When individual cancer types are evaluated across studies, the cumulative evidence seems to support the null. Leukemia may be the exception, with some indication of increased risk among multiple studies of air pollution. For cancer types other than hepatic cancer, the current study provides SMR-estimates that center on no risk and have narrow confidence bounds, providing inductive support for the frequentist null results. Incriminating areal-source HAP concentrations in childhood cancer has been and will continue to be difficult. It has been reasoned that more definitive prospective studies should utilize biomarkers to study the risks of prenatal exposures [24-26]. Two recent studies illustrate the utility of biomarkers for studies defining the complex causal relationships between fetal exposures to air pollution and adverse outcomes [25,26]. Such an approach may be useful to study childhood hepatic cancer around major Texas industrial facilities.

The current study supports the investigation of Hodgkin lymphoma and malignant bone tumors in areas of rapid population growth. Hodgkin lymphoma is often thought to be partly attributable to Epstein-Barr virus [29] and its reduced risk in rapidly growing

counties seems contradictory. Osteosarcoma, the most common malignant bone tumor in children [30] had a high probability of increased risk in counties with rapidly growing population. Both Hodgkin lymphoma and osteosarcoma are considered to be more common in teenagers. The population of cases in the current study may have been different than other studies because the current study followed children born in 1990 and later until the end of 2002 and, thus, would not have included any teenagers. The risks, increasing and decreasing, seen for these two cancers in rapidly growing counties should receive more study.

Infectious causes and population mixing have been proposed as causes of childhood cancer [27]. The theory is that densely populated regions have high levels of herd immunity but populations with constant population mixing are at increased risk for individuals. The purpose of the current study was to evaluate the use of population characteristics for focusing further study. Clark et al. [17] found excess risk when population growth was greater than 10% in an eleven-year period, thus our risk definition of 1% per year. The population mixing theory does not parse the risk for those moving into a region from those already residing in the region and thus, has only a population-based inference. For an individual deciding to move, the risks could be threefold. First, there could have been a geographic-based risk associated with the previous living location. Second, there could be a new geographic risk, at the new living location. Third, there could be a risk of being a mover. The full evaluation of these risks would be complex and require hierarchical modeling if the objective includes the estimation of risks interpretable at the individual mover level. The current study found median SMR

for measures of population density and population growth to be very near 1 with narrow 95% credible sets for most childhood cancer types.

Conclusions

Further study of childhood cancer in Texas could focus on germ cell tumors and “other” gliomas in areas of intense cropping, hepatic cancer near HAP release facilities and Hodgkin lymphoma and malignant bone tumors in counties with rapidly growing population.

Competing interests

The authors have no competing interests.

Authors' contributions

JT participated in the conception, design, analysis and drafted the manuscript. SC participated in the conception, data acquisition and helped draft the manuscript. LZ participated in the conception, design and analyses. All authors read and approved the final manuscripts.

Acknowledgements

Financial support provided by the National Institutes of Health and the National Cancer Institute through grants numbered R03 CA106080 and R03 CA119696

References

1. Lawson AB, Bohning D, Biggeri A, Lesaffre E, Viel J-F: **Disease Mapping and Its Uses.** In *Disease Mapping and Risk Assessment for Public Health*. Edited by Lawson A, Biggeri A, Bohning D, Lesaffre E, Viel J-F, Bertollini R. New York, NY: Wiley; 1999:3-13.
2. McNally RJQ, Eden TOB, Alexander FE, Kelsey AM, Birch JM: **Is there a common aetiology for certain childhood malignancies? Results of cross-space-time clustering analyses.** *Eur J Cancer* 2005, **41**: 2911-2916.
3. Thompson JA, Carozza SE, Zhu L: **An evaluation of spatial and multivariate covariance among childhood cancer histotypes in Texas (United States).** *Cancer Causes & Control* 2007, **18**: 105-113.
4. Infante-Rivard C, Weichenthal S: **Pesticides and childhood cancer: An update of Zahm and Ward's 1998 review.** *Journal of Toxicology and Environmental Health-Part B-Critical Reviews* 2007, **10**: 81-99.
5. Nasterlack M: **Pesticides and childhood cancer: An update.** *International Journal of Hygiene and Environmental Health* 2007, **210**: 645-657.
6. Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Harnly ME: **Childhood cancer and agricultural pesticide use: An ecologic study in California.** *Environ Health Perspect* 2002, **110**: 319-324.

7. Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Harnly M, Hertz A:
Agricultural pesticide use and childhood cancer in California. *Epidemiology*
2005, **16**: 93-100.
8. Reynolds P, Von Behren J, Gunier R, Goldberg DE, Hertz A: **Agricultural
pesticides and lymphoproliferative childhood cancer in California.** *Scand J
Work Environ Health* 2005, **31**: 46-54.
9. Schreinemachers DM: **Cancer mortality in four northern wheat-producing
states.** *Environ Health Perspect* 2000, **108**: 873-881.
10. Schreinemachers DM, Creason JP, Garry VF: **Cancer mortality in agricultural
regions of Minnesota.** *Environ Health Perspect* 1999, **107**: 205-211.
11. Knox EG, Gilman EA: **Spatial clustering of childhood cancers in Great Britain.**
J Epidemiol Community Health 1996, **50**: 313-319.
12. Knox EG, Gilman EA: **Migration patterns of children with cancer in Britain.** *J
Epidemiol Community Health* 1998, **52**: 716-726.
13. Knox EG: **Childhood cancers, birthplaces, incinerators and landfill sites.** *Int J
Epidemiol* 2000, **29**: 391-397.
14. Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Smith DF:
**Childhood cancer incidence rates and hazardous air pollutants in California:
An exploratory analysis.** *Environ Health Perspect* 2003, **111**: 663-668.

15. Raaschou-Nielsen O, Reynolds P: **Air pollution and childhood cancer: A review of the epidemiological literature.** *International Journal of Cancer* 2006, **118**: 2920-2929.
16. McNally RJQ, Eden TOB: **An infectious aetiology for childhood acute leukaemia: a review of the evidence.** *British Journal of Haematology* 2004, **127**: 243-263.
17. Clark BR, Ferketich AK, Fisher JL, Ruymann FB, Harris RE, Wilkins JR: **Evidence of population mixing based on the geographical distribution of childhood leukemia in Ohio.** *Pediatric Blood & Cancer* 2007, **49**: 797-802.
18. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P: **International classification of childhood cancer, third edition.** *Cancer* 2005, **103**: 1457-1467.
19. Spiegelhalter D, Thomas A, Best N, Lunn D: *WinBUGS User Manual: Version 1.4.* Cambridge: MRC Biostatistics Unit; 2003.
20. Thomas A, Best N, Lunn D: *GeoBUGS User Manual Version 1.2.* Cambridge: MRC Biostatistics Unit; 2003.
21. Kettles MA, Browning SR, Prince TS, Horstman SW: **Triazine herbicide exposure and breast cancer incidence: An ecologic study of Kentucky counties.** *Environ Health Perspect* 1997, **105**: 1222-1227.

22. Buka I, Koranteng S, Vargas ARO: **Trends in childhood cancer incidence: Review of environmental linkages.** *Pediatric Clinics of North America* 2007, **54**: 177-203.
23. Buffler PA, Kwan ML, Reynolds P, Urayama KY: **Environmental and genetic risk factors for childhood leukemia: Appraising the evidence.** *Cancer Invest* 2005, **23**: 60-75.
24. Maisonet M, Correa A, Misra D, Jaakkola JJK: **A review of the literature on the effects of ambient air pollution on fetal growth.** *Environ Res* 2004, **95**: 106-115.
25. Perera FP, Rauh V, Whyatt RM, Tsai WY, Bernert JT, Tu YH *et al.*: **Molecular evidence of an interaction between prenatal environmental exposures and birth outcomes in a multiethnic population.** *Environ Health Perspect* 2004, **112**: 626-630.
26. Perera FP, Tang DL, Tu YH, Cruz LA, Borjas M, Bernert T *et al.*: **Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage.** *Environ Health Perspect* 2004, **112**: 1133-1136.
27. Kinlen L: **Childhood leukaemia and ordnance factories in west Cumbria during the Second World War.** *British Journal of Cancer* 2006, **95**: 102-106.
28. SEER: *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995.* Bethesda, MD: National Cancer Institute, SEER Program; 1999.

29. Landgren O, Caporaso NE: **New aspects in descriptive, etiologic, and molecular epidemiology of Hodgkin's lymphoma.** *Hematology-Oncology Clinics of North America* 2007, **21**: 825-+.

30. Buckley JD, Pendergrass TW, Buckley CM, Pritchard DJ, Nesbit ME, Provisor AJ *et al.*: **Epidemiology of osteosarcoma and Ewing's sarcoma in childhood - A study of 305 cases by the Children's Cancer Group.** *Cancer* 1998, **83**: 1440-1448.

Figures

Figure 1 - Frequency distribution of county-year population growth rates.

Figure 2 - Frequency distribution of county-year release of hazardous air pollutants.

Figure 3 - Frequency distribution of county-year cropping intensity for total corn, sorghum, wheat and cotton.

Figure 4 – Study-specific temporal effects

Table 1 - Standard Morbidity Ratios for county characteristics of the mother's living location at the time of birth. Values are the median and 95% credible sets from the posterior distribution.

	CROPS	HAPS	METRO	URBAN	GROWTH
Acute Lymphoid leukemias (ALL)	1.01 (0.79, 1.28)	0.97 (0.76, 1.25)	1.04 (0.82, 1.36)	1.11 (0.82, 1.48)	0.97 (0.82, 1.16)
Acute myeloid leukemias (AML)	0.75 (0.41, 1.27)	0.81 (0.50, 1.29)	0.97 (0.61, 1.58)	1.01 (0.57, 1.84)	1.22 (0.87, 1.81)
Other leukemias	0.98 (0.50, 1.80)	0.57 (0.31, 1.02)	1.26 (0.66, 2.51)	1.60 (0.73, 3.71)	0.95 (0.58, 1.50)
Hodgkin lymphoma	1.00 (0.41, 2.36)	0.81 (0.35, 2.02)	1.03 (0.49, 2.40)	1.47 (0.52, 4.96)	0.49 (0.27, 0.96)
Non-Hodgkin lymphoma	1.02 (0.61, 1.70)	0.75 (0.48, 1.17)	1.10 (0.70, 1.77)	1.16 (0.68, 2.11)	0.88 (0.63, 1.26)
Ependymoma and choroid plexus tumor	0.56 (0.26, 1.12)	1.07 (0.59, 1.99)	0.90 (0.51, 1.60)	0.97 (0.46, 2.26)	0.86 (0.54, 1.39)
Astrocytomas	0.97 (0.67, 1.40)	0.80 (0.57, 1.15)	1.22 (0.85, 1.78)	1.07 (0.69, 1.71)	1.03 (0.79, 1.43)
Intracranial and intraspinal embryonal tumors	0.72 (0.43, 1.24)	1.12 (0.71, 1.77)	0.85 (0.55, 1.35)	1.42 (0.74, 2.80)	0.99 (0.69, 1.44)
Other gliomas	1.77 (0.98, 3.27)	1.41 (0.82, 2.54)	1.23 (0.69, 2.25)	1.08 (0.48, 2.72)	1.03 (0.64, 1.69)
Other CNS tumors	1.04 (0.57, 1.83)	0.94 (0.56, 1.55)	1.29 (0.78, 2.16)	0.82 (0.44, 1.65)	0.82 (0.57, 1.20)
Neuroblastoma and other peripheral nervous cell tumors	1.12 (0.78, 1.60)	1.15 (0.83, 1.59)	1.11 (0.81, 1.64)	0.74 (0.52, 1.09)	0.93 (0.74, 1.17)
Rtinoblastoma	0.86 (0.50, 1.48)	1.02 (0.60, 1.60)	1.22 (0.77, 1.99)	1.05 (0.58, 2.00)	0.89 (0.62, 1.32)
Renal tumors	0.95 (0.59, 1.51)	1.21 (0.80, 1.79)	1.04 (0.69, 1.61)	0.98 (0.58, 1.69)	0.91 (0.66, 1.28)
Hepatic tumors	0.80 (0.32, 1.91)	1.87 (0.95, 3.98)	0.99 (0.53, 1.90)	1.28 (0.46, 4.61)	1.16 (0.66, 2.18)
Malignant bone tumors	1.31 (0.51, 2.90)	1.15 (0.55, 2.55)	0.77 (0.36, 1.75)	0.67 (0.24, 2.08)	1.86 (0.89, 4.24)
Soft tissue and other extraosseous sarcomas	1.03 (0.64, 1.59)	0.86 (0.59, 1.28)	1.06 (0.70, 1.62)	1.42 (0.83, 2.57)	1.04 (0.74, 1.41)
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	1.54 (0.90, 2.75)	0.86 (0.50, 1.46)	1.40 (0.82, 2.64)	0.87 (0.46, 1.77)	1.03 (0.66, 1.63)
Other malignant epithelial neoplasms and melanomas	1.25 (0.57, 3.05)	0.89 (0.42, 1.97)	1.23 (0.60, 2.87)	0.98 (0.38, 3.01)	1.17 (0.66, 2.25)
Other and unspecified malignant neoplasms (including uncoded)	0.85 (0.25, 2.30)	0.68 (0.25, 1.75)	1.07 (0.47, 2.88)	1.17 (0.37, 4.83)	0.81 (0.37, 1.88)

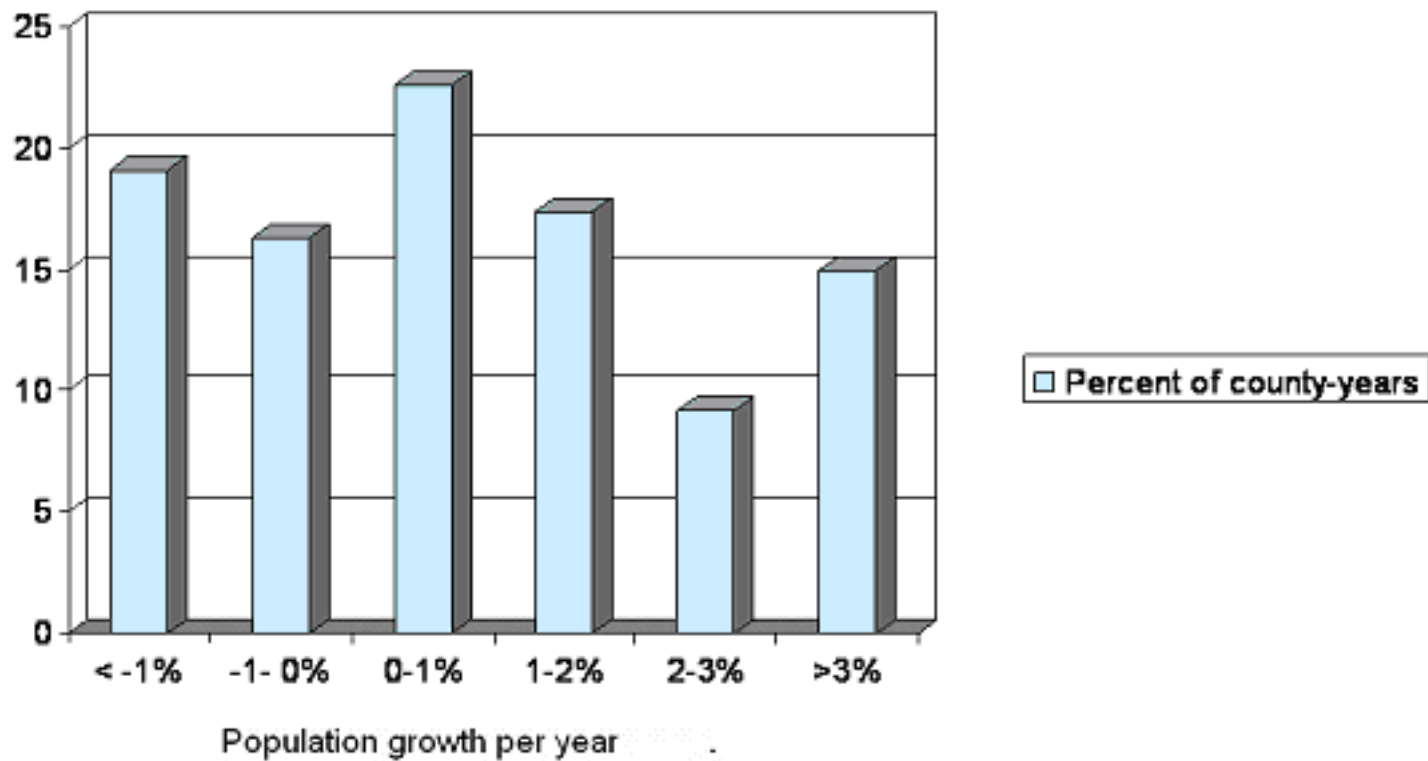


Figure 1

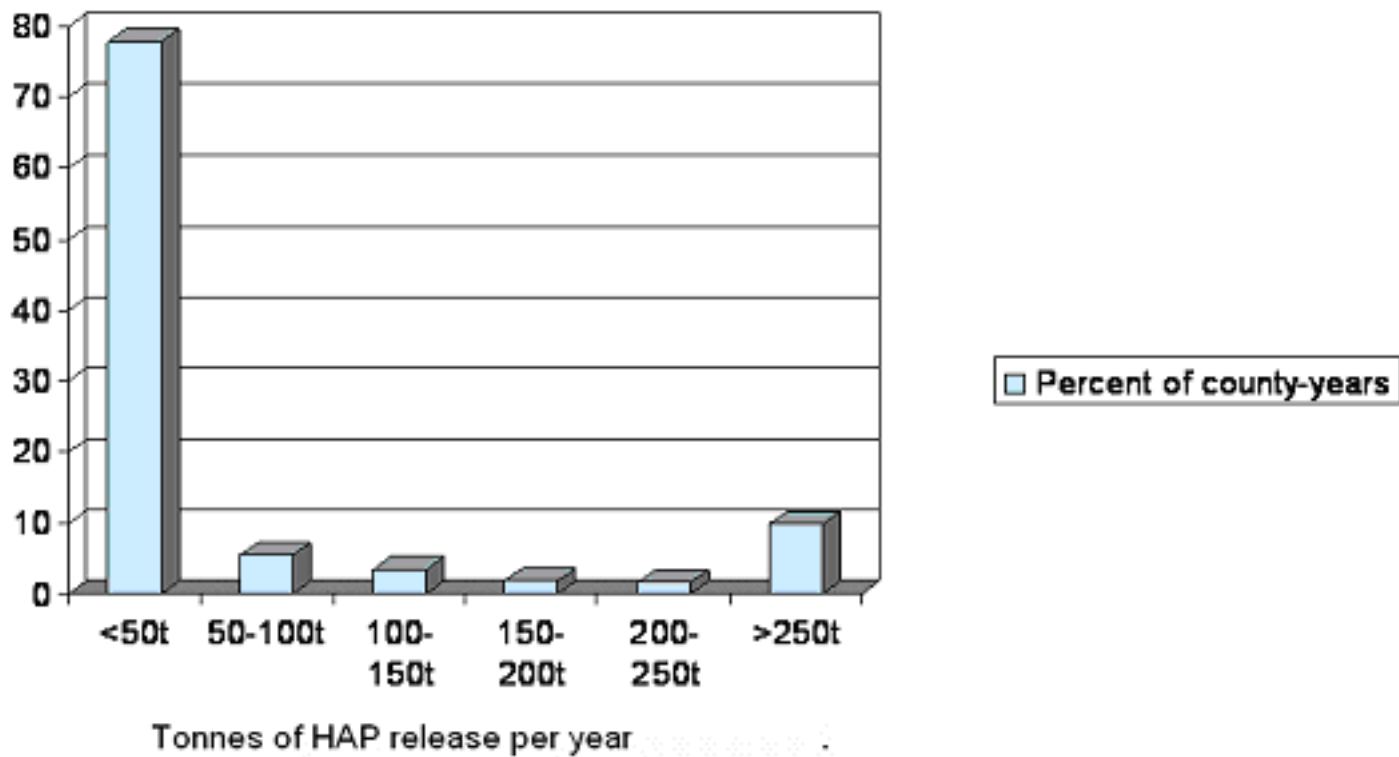


Figure 2

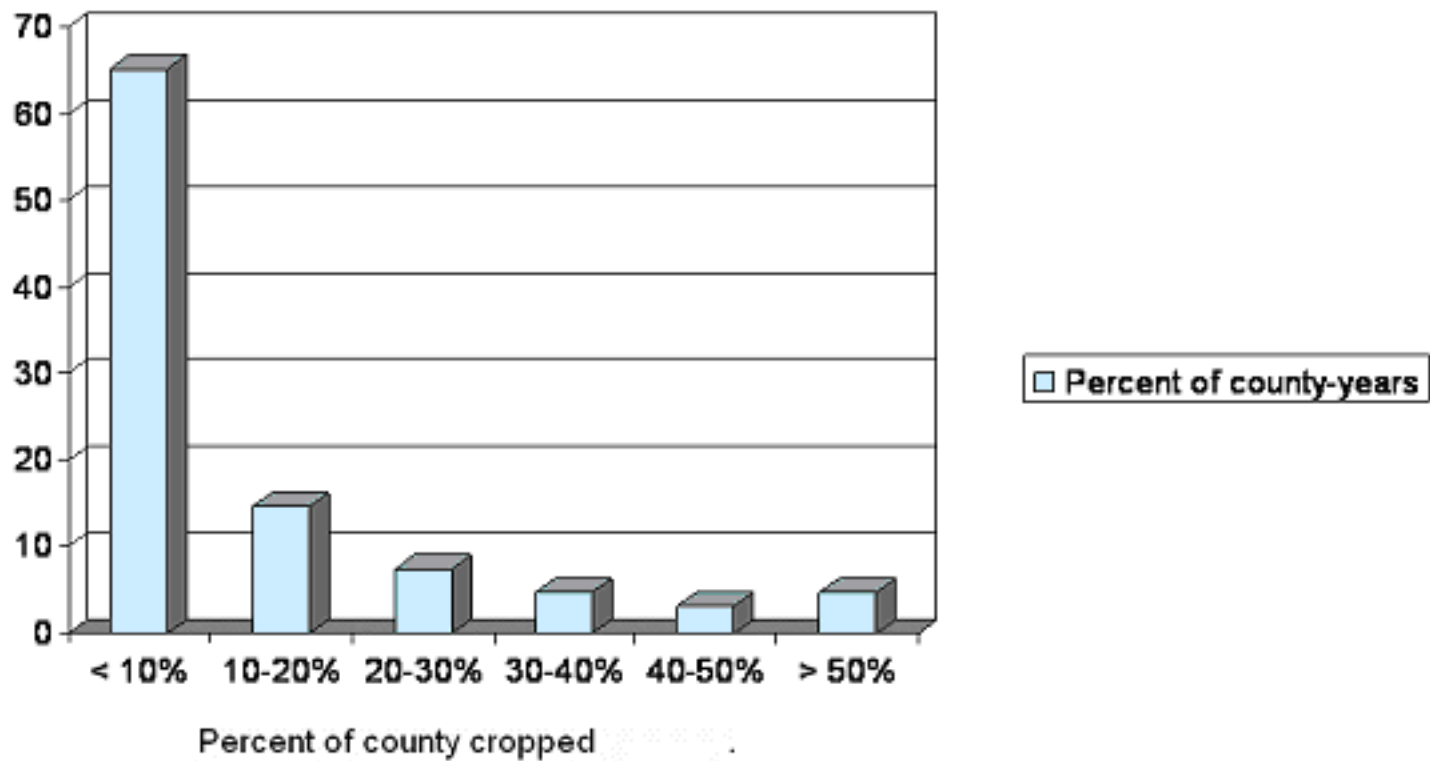


Figure 3

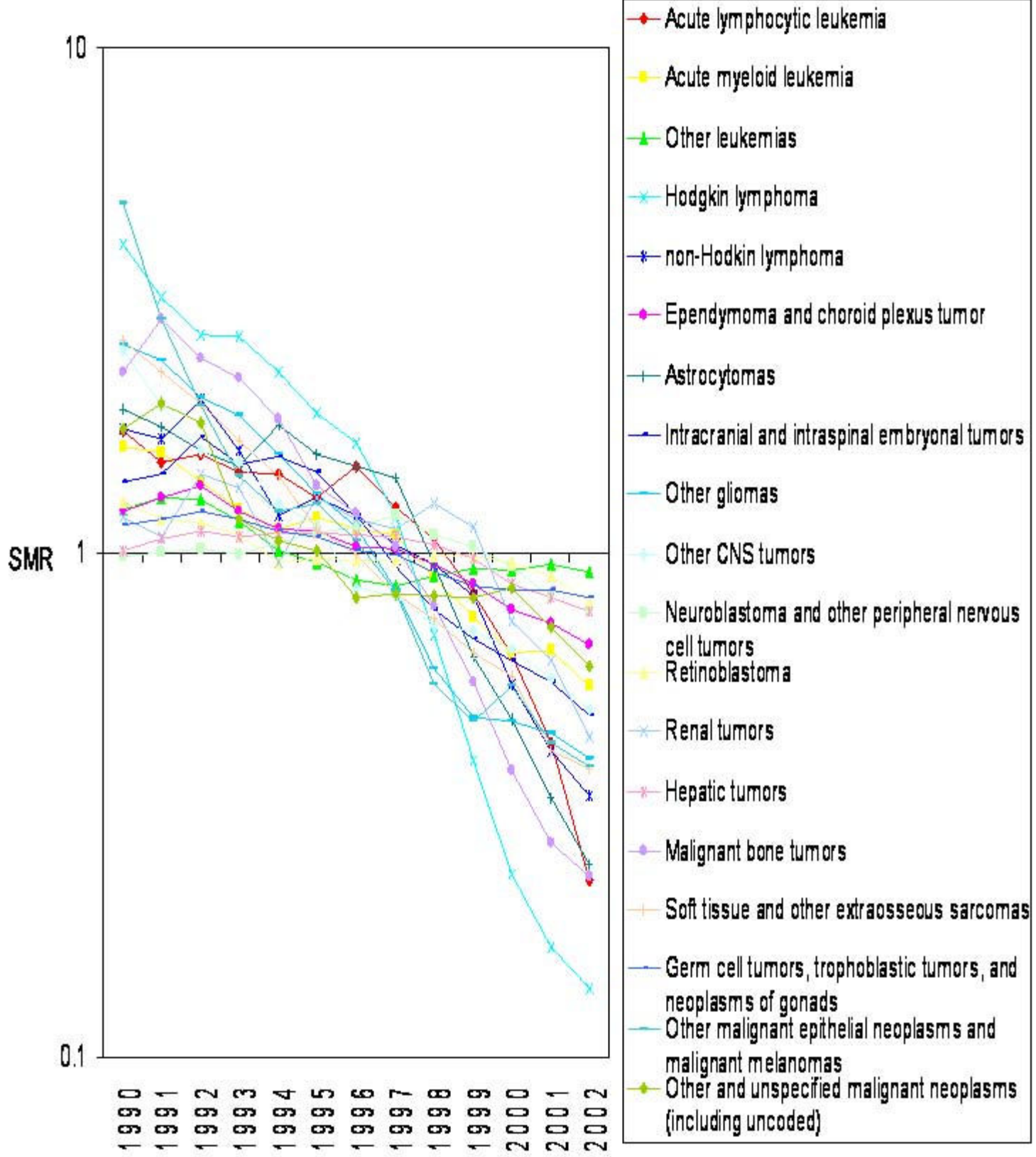


Figure 4