Hierarchical Modeling and Other Spatial Analyses in Prostate Cancer Incidence Data

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Background: State central cancer registries are often asked to respond to questions about the spatial distribution of cancer cases. Spatial analysis methods and technology are evolving rapidly, and can be a considerable challenge to registries that do not have staff with training in this area. The purpose of this article is to describe a general methodological approach that potentially might be a starting point for many cancer registry spatial analyses at the county level.

Methods: Prostate cancer incident cases (N=31,159) from the Louisiana Tumor Registry from 1988 to 1999 were used for illustrative purposes. To explore spatio-temporal patterns, analyses focused on four time periods, each 3 years in length: 1988–1990, 1991–1993, 1994–1996, and 1997–1999. For each time period, race-specific (white and black), direct age-adjusted incidence rates and indirect standardized incidence ratios (SIRs) were calculated, smoothed using Bayesian methods, and assessed for evidence of spatial autocorrelation using global and local Moran's I. Hierarchical generalized linear models (HGLM) were fitted to identify significant covariates. Clusters of elevated and lower rates were identified using a spatial scan statistic (SaTScan™).

Results: Temporal trends in SIRs in both race groups were consistent with the introduction of prostate specific antigen (PSA) testing in Louisiana during the late 1980s and early 1990s, but possibly with a lag in black males. Clusters of lower than expected values were observed for white males in the central (p =0.001) and southeastern coastal areas (p =0.001), and to a greater extent for black males in the central (p =0.001), southwestern and southeastern coastal parishes (p =0.001).

Conclusions: Mapping disease occurrence by time period is an effective way to explore spatio-temporal patterns. HGLM models and software are available to control for covariates and for unstructured and spatially structured variability that may confound spatial variability patterns.

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Introduction

With the establishment of a population-based central cancer registry in every state, there is an increasing advocacy for the use of registry data. Registry staffs are often asked to respond to questions about the spatial distribution of cancer cases. A few examples of potential questions[1] might include: Does a map of county-level cancer incidence suggest that clusters are present? How do spatial patterns change over time? Where do cancer prevention and control efforts need to be focused?

Responding to these types of questions can be a considerable challenge for cancer registry staff because a relatively large number of spatial analytic methods and tools exist, registries may not have a spatial statistician easily available, different spatial methods may give somewhat different results, and more than one spatial method may be needed to more fully address a spatial question.

The purpose of this article is to illustrate a six-part methodologic approach that might be a useful starting point for many cancer registry spatial analyses at the county level. Highlights are as follows: (1) to help stabilize estimates for rural counties with smaller numbers but enable insights into changes in spatial patterns over time, analyze time periods with at least 3 years of data; (2) calculate and map both direct age adjusted

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rates and indirect standardized incidence ratios (SIRs) for each of the 3-year periods; (3) construct full Bayesian smoothed estimates to enhance any visual appearance of county clusters; (4) use global and local Moran's I statistics to evaluate autocorrelation and outliers; (5) carry out hierarchical modeling to remove the effect of significant confounders or covariates; and (6) employ a spatial scan statistic to identify county clusters with elevated or decreased risk, after controlling for the significant covariates and spatial autocorrelation.

This methodologic approach is illustrated with a parish-(the Louisiana equivalent of a county) level analysis of incident prostate cancer cases reported to the Louisiana Tumor Registry (LTR) during the 12-year period, 1988 to 1999. Established risk factors for prostate cancer include only age and race. Other factors such as genetic susceptibility, diet, and physical inactivity are currently being investigated. Incidence rates are 61% higher in black males than in white males[2] and increase sharply after age 40. United States incidence rates have shown to be positively correlated with prostate specific antigen (PSA) test screening at the state level.[3] Because PSA testing was introduced and then increasingly used in Louisiana during the late 1980s and early 1990s, a key question might be: After adjusting for age and race and removing the effect of significant confounders or covariates, what were Louisiana parish prostate cancer incidence spatial patterns, during and after the introduction of PSA testing?

Table 1. Study variables and their abbreviations

Abbreviation	Variable description
ALHS	Percent of persons who did not complete high school (parish)
AGE	Number of males (race-specific) in an age group in a parish
AGE GROUPS	Age group category Group 1: 30–34 Group 2: 35–39 Group 3: 40–44 Group 4: 45–49 Group 5: 50–54 Group 6: 55–59 Group 7: 60–64 Group 8: 65–69 Group 9: 70–74 Group 10: 75–79 Group 11: 80–74 Group 12: 85+
DRE	Percent of persons who had a digital/rectal exam in the last 2 years in a region (containing three or more parishes)
PHYS	Number of a physicians in a parish
PHYSC	Number of physicians per capita in a parish
PXX	Proportion of males of age xx or greater among those aged 30 years and older in a parish (xx=55, 60, 65, 70, 75, 80, 85)
YEAR	Year of diagnosis (single year)
YEARGRP	Year of diagnosis group Group 1: 1988–1990 Group 2: 1991–1993 Group 3: 1994–1996 Group 4: 1997–1999

Methods

Study Variables and Data Sources

Prostate cancer incident cases. All incident prostate cancer cases (N=31,159) diagnosed among Louisiana white and black males aged 30 years and older from 1988 to 1999 were identified by the LTR, a participant of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and the CDC's National Program of Cancer Registries (NPCR). The residential address at time of diagnosis for each case was reviewed and assigned a parish Federal Information Processing Standards (FIPS) code number, and also latitude–longitude coordinates corresponding to the center (centroid) of each parish.

Population estimates. Louisiana parish-specific population estimates for white and black males by 5-year age groups for the 12-year study period (1988–1999) were obtained from the SEER program, based on Census Bureau estimates.[4,5] These parish population estimates incorporated bridged single-race estimates that were derived from the original multiple-race categories in the 2000 Census and also included the 1990–2000 intercensal revision.

Education level. The proportion of individuals 25 years and older with less than a high school education in a parish (ALHS) (Table 1) was used as a surrogate variable for socioeconomic status (SES). Data were obtained for each parish from the 1990 U.S. Census.[6]

Active physician licenses per capita. Physicians with an active license during the study period[7] (1988–1999) were used to compute the total number of physicians and physicians per capita as a surrogate variable for access to health care at the parish level.

Digital rectal exams. Behavioral Risk Factor Surveillance System (BRFSS)[8] survey data for Louisiana during the study period did not include specific questions about PSA testing. However, data for the proportion of the population receiving a digital rectal examination (DRE) within the last 2 years for white and black males 50 years and over were available for the 1991, 1993, 1994, 1995, and 2001 surveys (Table 1). These data were interpolated to estimate DRE in regions consisting of at least three parishes for each year of diagnosis group (Table 1), and then were modeled to develop parish-specific DRE estimates.

Data Analyses

Aggregation by year of diagnosis. To evaluate spatiotemporal trends, prostate cancer cases and population estimates were grouped into four time periods (YEARGRP) (Table 1). Each of these time periods was 3 years in length:

1988–1990 (Time Period 1), 1991–1993 (Time Period 2), 1994–1996 (Time Period 3), and 1997–1999 (Time Period 4).

Standardized rates and ratios. Direct age-adjusted (U.S. 2000 standard million)[9] parish-level incidence rates were computed. Because the male population 30 years and older was used[10] in the denominator rather than the standard million of all ages, the age-adjusted incidence rates were inflated by about 42%. Statewide age-specific rates pooled over the entire study period formed the internal standard used to compute the expected numbers for indirect SIRs.

Display of spatio-temporal patterns for standardized rates and ratios. The prostate cancer direct age-adjusted incidence rates and SIRs were mapped using the four study time periods (YEARGRP) (Table 1), with suppression of rates in parishes with less than six cases in a time period. Six cut-points included the entire range of the direct adjusted rates for the first time period (1988–1990) (Table 1). These cut-points were used to map the other direct adjusted time periods (Figure 1).

For maps of SIRs, seven 30-unit intervals were established (Figure 2). These were centered at 100% including open intervals at each end. The central interval (85% to 115%) indicated those parishes having SIRs near their expected values. Parishes above (or below) this interval had higher (or lower) SIRs than expected.

Bayesian map smoothing

Disease incidence maps[11–13] were smoothed by fitting a full Bayesian model using a Gibbs Markov Chain Monte Carlo (MCMC) algorithm[14,15] with the WinBUGS software using a spatial conditional autoregression (CAR) model (Figure 3).[16–21] The CAR model replaced the random effect in an area with the average of the random effects in its surrounding contiguous areas.

Identification of spatial autocorrelation. The global Moran's I was used to test for significant global autocorrelation for each time period. Corresponding 95% confidence intervals (CI) were calculated.[22–24]The local Moran test[25] was used to identify significant clustering and spatial outliers in the unsmoothed age-adjusted SIRs. Parish-specific effects were computed for each time period using GeoDa software (Spatial Analysis Laboratory, University of Illinois at Urbana–Champaign, Illinois) with the weights corresponding to the five nearest parish centroids. LISA (local indicators of spatial association) significance (5% level) maps were constructed to identify spatial clusters and outliers (Figure 4). Parishes were categorized by the type of spatial autocorrelation as: (1) high-high or low-low clusters, defined as a parish with a high (low) rate surrounded by neighbors with high (low) rates, or (2) low–high or high–low spatial outliers, defined as a parish with a low (high) rate surrounded by parishes with high (low) rates.

Hierarchical statistical modeling and covariate adjustment. A hierarchical model provides a way to estimate covariate effects while controlling for variability in the form of parish-specific random effects and spatio-temporal autocorrelation. The hierarchical nature of the model arises from the inclusion of random parish effects that can be assumed to be drawn from a larger population.

The Hierarchical General Linear Model (HGLM) models the number of cases, assumed to follow a Poisson distribution, as

$$\log(O_i) = \gamma + \sum_{j=1}^{p} \beta_j X_{ij} + u_i + e_i + \log(T_i), \qquad (1)$$

where $i = 1, 2, \ldots$ 64th parish, O_i are the observed number of cases, γ is an overall intercept; X_{ij} are the parish-specific characteristics; β_j are their associated coefficients; u_i are the random (unstructured, noise) effects assumed to be normally distributed with mean 0 and variance τ_0^2; e_i are the spatially correlated errors; and T_i are the offsets defined either as the parish-level expected number of cases or parish-level population counts.[26]

Time trends were evaluated by including time as a categorical covariate, setting the offsets to the age-adjusted parish-specific expected values and using the temporal lag model as an autoregressive covariate structure. Inclusion of the spatial-exponential covariance structure provides a model for autocorrelation that is inversely proportional to the Euclidian distance between parish centroids. The SAS Glimmix procedure (SAS, Cary NC) was used to carry out these analyses.[27–30]

Scan statistic analyses to identify clusters. The Poisson version of Kulldorff's scan statistic (SaTScan™ version 5.1, Kulldorff and Information Management Services, Inc., developed under the joint auspices of (i) Martin Kulldorff, (ii) the National Cancer Institute, and (iii) Farzad Mostashari at the New York City Department of Health and Mental Hygiene. Boston, MA, and New York, NY)[31–33] was used to identify clusters of high or low risk, adjusting for significant covariates.[32,33] Race-specific "adjusted" expected numbers of prostate cancer cases were computed for each parish for the four time periods, using the model given by Equation (1). The observed and "adjusted" expected cases were aggregated over all time periods and used to compute the SIRs as input data for the cluster analysis. Parish centroids were used as cluster centers, and an upper limit of 50% of the population at risk was used to allow for geographically overlapping clusters. Monte Carlo simulations (999) were used for significance testing with a significance level of 0.05. Primary and secondary clusters with significance levels below the 5% level were identified. For purposes of this study, secondary clusters were reported and mapped only if the centroid of the secondary cluster was not contained in a previously reported cluster (i.e., whereas the spatial boundaries of two clusters might have some overlap, the centroids of two clusters could not be contained within the boundaries of one of the clusters).

Results

Directly adjusted incidence rates. Figure 1 shows maps of directly age-adjusted incidence rates for the four time periods, for white and black males. In each time period, black males had consistently higher prostate cancer rates than white males, a pattern observed nationwide. Lower incidence rates for both races were found primarily in central Louisiana in 1988–1990. Elevated rates for white males were found in parishes along the northern Louisiana–Arkansas border and the southeastern (Baton Rouge area) in 1991–1993 and remained high in 1994–1996. Higher rates were found

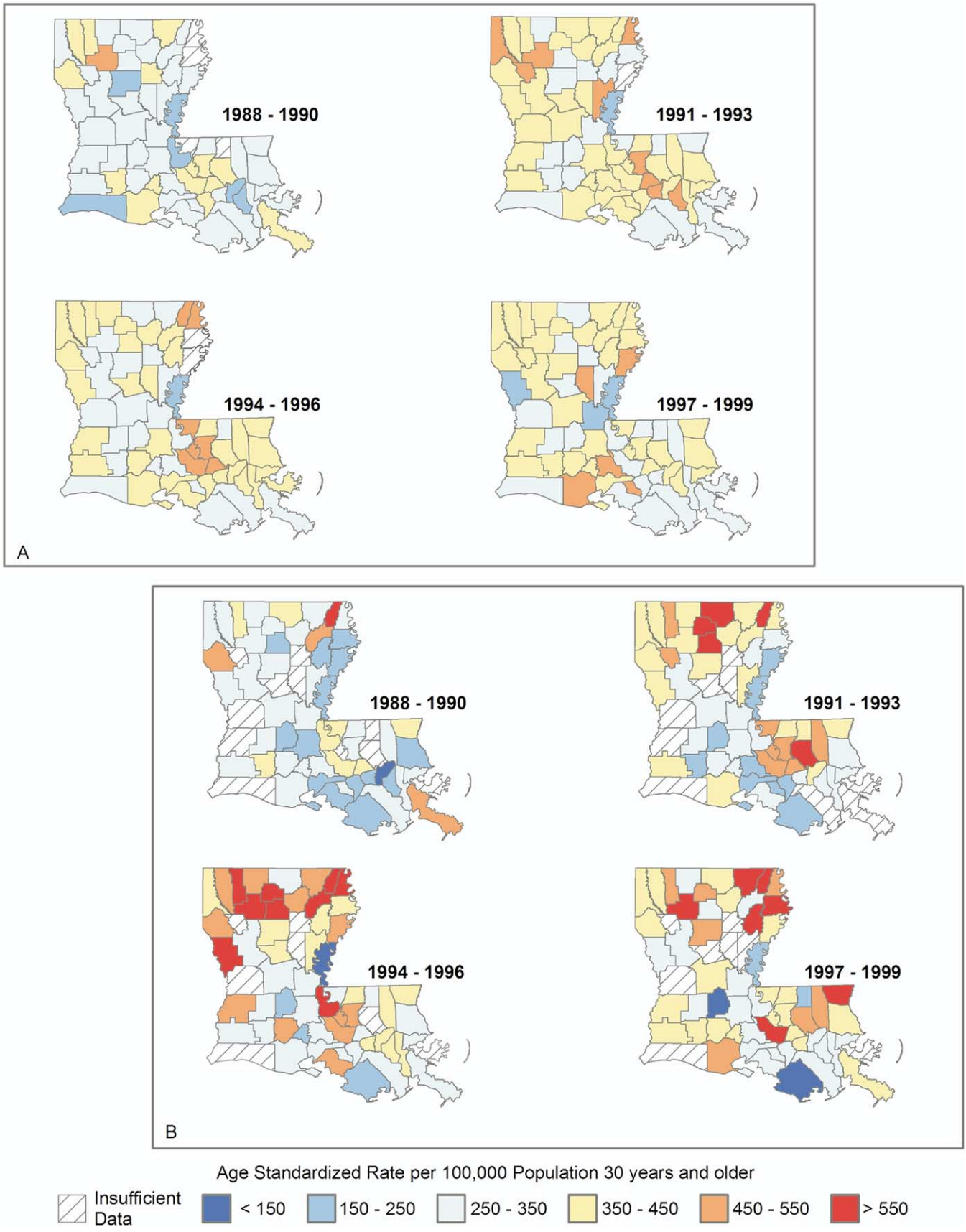

Figure 1. Average annual age-standardized prostate cancer incidence rates (all stages) per 100,000 population at least 30 years of age for four time periods in Louisiana parishes. The rates were direct standardized to the U.S. 2000 standard population at least 30 years of age. (**A**) White males. (**B**) Black males.

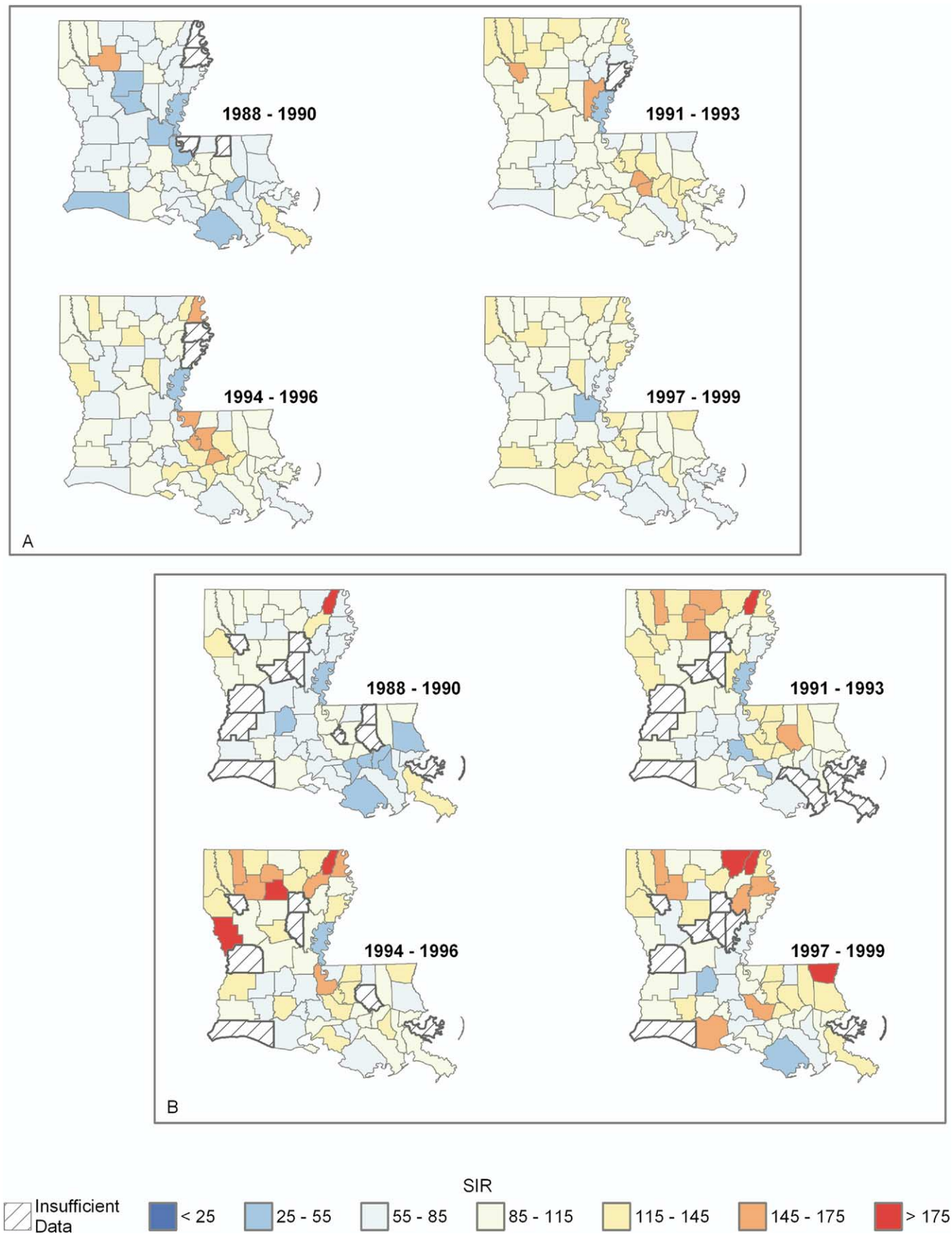

Figure 2. Indirect standardized prostate cancer incidence ratios (SIRs) (all stages) among men at least 30 years of age for four time periods in Louisiana parishes. The internal standard is the Louisiana race-age specific incidence rates over the entire time period. (**A**) White males. (**B**) Black males.

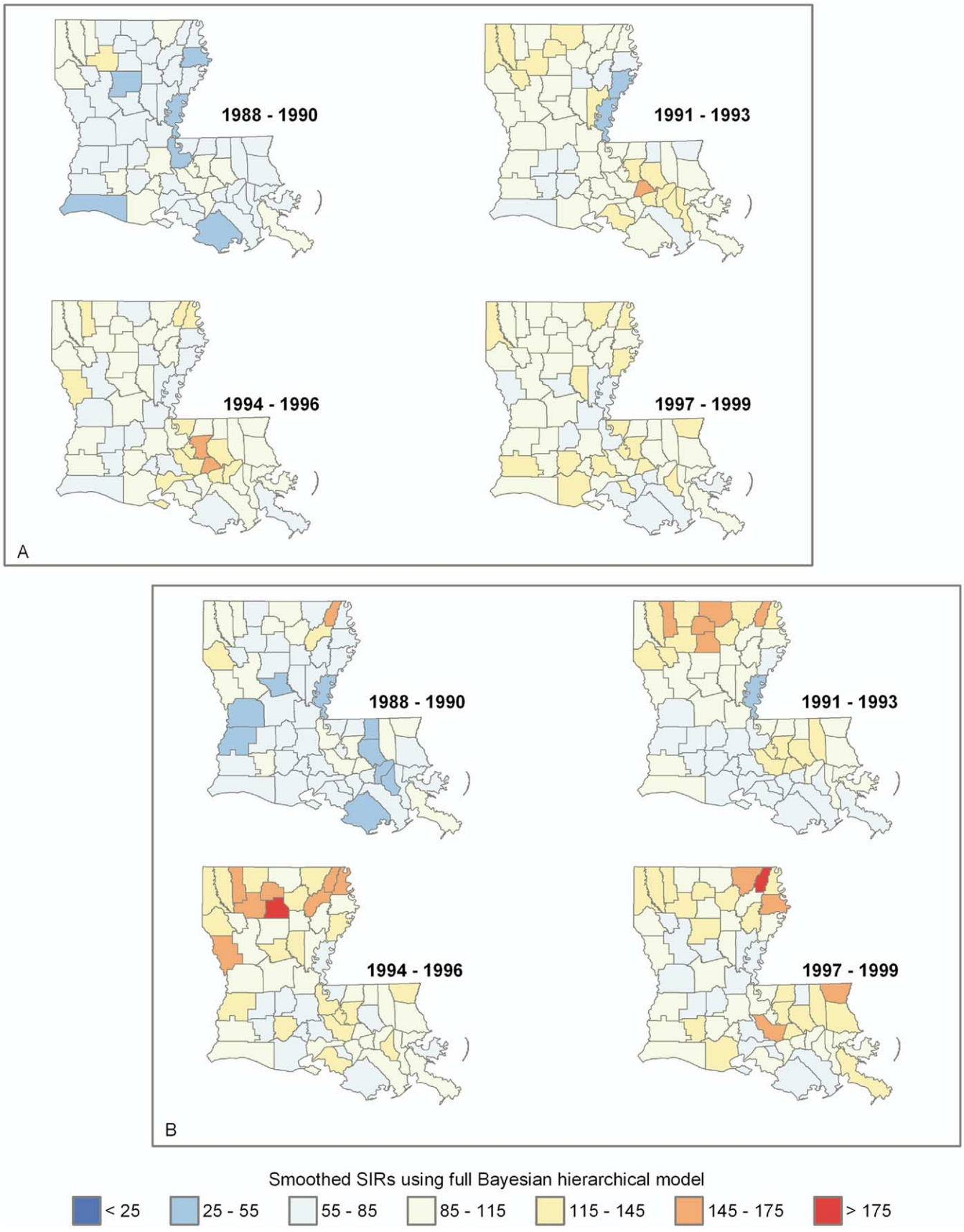

Figure 3. Smoothed standardized prostate cancer incidence ratios (SIRs) (all stages) among men at least 30 years of age for four time periods in Louisiana parishes, using a full Bayesian hierarchical model. (**A**) White males. (**B**) Black males.

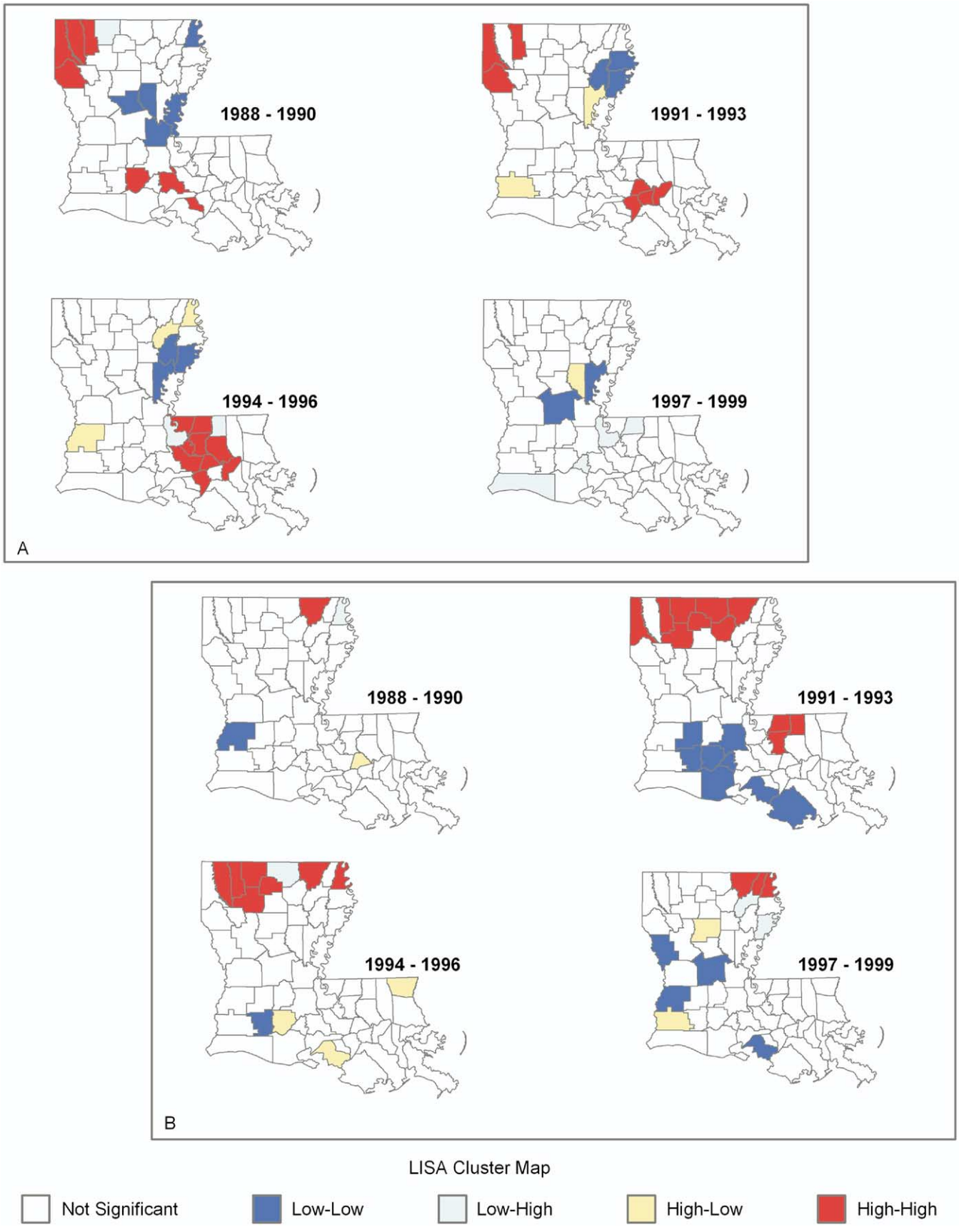

Figure 4. Univariate LISA maps of local Moran statistics based on unsmoothed age-adjusted prostate cancer SIRs for four time periods in Louisiana parishes. This approach identifies high–high (low–low) clusters, defined as a parish with a high (low) value surrounded by other parishes with high (low) values. It also identifies high–low (low–high) spatial outliers, defined as a parish with a high (low) value surrounded by parishes with low (high) values. (**A**) White males. (**B**) Black males.

for black males in northern parishes and the Baton Rouge area in 1991–1993, 1994–1996, and 1997–1999. Lower incidence rates among black males were found primarily in central Louisiana and southeastern coastal parishes.

Indirectly adjusted SIRs. Figure 2 shows maps of parish-specific SIRs for both races. Using an upper cutpoint (SIR>115%) areas of high incidence were found in the upper southeastern state whereas areas of low incidence (SIR<85%) were identified in central and southeastern parishes (1997–1999).

The observed changes over time were consistent with the national trend toward increased prostate cancer incidence, after the introduction of the PSA screening test. For example, among white males (Figure 2A), SIRs were lowest in Time Period 1 (1988–1990), and Time Period 4 (1997–1999) was significantly higher than Time Period 1 (1988–1990) ($p<0.001$). The difference between Time Period 2 (1991–1993) and Time Period 4 (1997–1999) was of borderline significance ($p=0.16$), whereas the difference between Time Period 3 (1994–1996) and Time Period 4 (1997–1999) was insignificant ($p=0.5$).

Among black males (Figure 2B), areas of high SIR (>115%) were located at the northeast and northwest corners of the state as well as the upper southeastern portion. Areas of low incidence (SIR<85%) were observed in the central, south central and southeastern coastal parishes. Similar to national trends after the introduction of PSA testing, SIRs also were lowest in Time Period 1 (1988–1990), and Time Period 4 (1997–1999) was significantly higher than Time Period 1 (1988–1990) ($p<0.001$). The difference between Time Period 2 (1991–1993) and Time Period 4 (1997–1999) was of borderline significance ($p=0.20$), and that between Time Period 3 (1994–1996) and Time Period 4 (1997–1998) was insignificant ($p=0.61$).

Bayesian map smoothing. Figure 3 shows SIR maps by race, after smoothing by full Bayesian methods. The Figure 3 spatial patterns generally are similar to those observed with the directly adjusted incidence rates (Figure 1) and the indirectly standardized SIRs (Figure 2). The Bayesian smoothing of SIRs for a particular area tended to yield an estimate closer to the area average. Bayesian smoothing of SIRs did not alter the temporal trends observed in Figure 2.

Autocorrelation and outliers. Moran's global I statistics and its corresponding 95% CI are shown by race and time period in Table 2. Positive, significant, spatial autocorrelation of SIRs was observed among white males in the Time Periods 2 and 3 (1991–1993, 1994–1996), with borderline positive spatial autocorrelation in Time Period 1 (1988–1990). Among black males, positive, significant spatial autocorrelation was observed in Time Period 2 (1991–1993), with borderline positive spatial autocorrelation in Time Period 4 (1997–1998).

Table 2. Spatial autocorrelation of prostate cancer incidence by race, as measured by Moran's I statistic

Time period	White (95% CI)	Black (95% CI)
1988–1990	0.13 (−0.00–0.25)	0.05 (−0.08–0.18)
1991–1993	0.21 (0.08–0.34)	0.30 (0.16–0.42)
1994–1996	0.21 (0.09–0.33)	0.07 (−0.06–0.19)
1997–1999	0.01 (−0.12–0.14)	0.12 (−0.01–0.25)

95% CI=I±1.96 · SE.

Figure 4 shows Moran's univariate local indicator of spatial autocorrelation (LISA) by race for each time period. Clusters with higher than expected incidence among white males were identified in the northwestern and the south central parishes (1988–1990, 1991–1993), and in the southeastern parishes (1994–1996). Clusters with lower than expected incidence were identified in some portions of the east central region in all time periods. Among black males, higher than expected incidence was observed in the northern Louisiana–Arkansas border parishes in the last three time periods (1991–1993, 1994–1996, 1997–1999) and in the north Baton Rouge region (1991–1993). Lower than expected incidence was evident in the south-central region during the second period (1991–1993).

Spatial Association

Covariate adjustment controlling only for unstructured variation. The final hierarchical generalized linear models (HGLM) (Equation [1]) for white males showed increasing prostate cancer incidence was significantly associated with increasing numbers of white males in an age group in a parish (AGE) ($p<0.0001$), decreasing (single) year of diagnosis (YEAR) ($p<0.0001$), and decreasing percent of persons who did not complete high school in the parish (ALHS) ($p=0.0003$) (Table 3), suggesting that these variables were significantly associated with prostate cancer incidence. The proportion of white males aged 55 or older (among those aged 30 years and older) in a parish (P55) was of borderline significance ($p=0.078$). The number of a physicians in a parish (PHYS), the number of physicians per capita in a parish (PHYSC), and the percent of persons who had a digital rectal exam (DRE) in the last 2 years in a region (containing three or more parishes) were not associated with prostate cancer incidence in white males ($p>0.20$).

For black males, increasing prostate cancer incidence was significantly associated with increasing numbers of black males in an age group in a parish (AGE) ($p<0.0001$), decreasing (single) year of diagnosis (YEAR) ($p<0.0001$), increasing proportion of males of aged 85 or older (among those aged 30 years and older) in a parish (P85) ($p<0.0001$), and decreasing percent of persons who did not complete

Table 3. Hierarchical general linear modeling regression coefficients for white males

Variable	Estimate	SE	DF	*p*-value
Intercept	−4.55	0.04	62	<0.0001
Age				
85+	Reference			
30–34	−8.3	0.5	9139	<0.0001
35–39	−7.4	0.32	9139	<0.0001
40–44	−6.04	0.17	9139	<0.0001
45–49	−4.32	0.08	9139	<0.0001
50–54	−2.72	0.05	9139	<0.0001
55–59	−1.76	0.04	9139	<0.0001
60–64	−1.01	0.03	9139	<0.0001
65–69	−0.44	0.03	9139	<0.0001
70–74	−0.16	0.03	9139	<0.0001
75–79	−0.05	0.03	9139	0.1604
80–84	−0.02	0.04	9139	0.5348
Year of diagnosis				
1999	Reference			
1988	−0.33	0.04	9139	<0.0001
1989	−0.23	0.04	9139	<0.0001
1990	−0.08	0.03	9139	0.0133
1991	0.08	0.03	9139	0.0086
1992	0.2	0.03	9139	<0.0001
1993	0.11	0.03	9139	0.0003
1994	0.11	0.03	9139	0.0009
1995	0.02	0.03	9139	0.451
1996	0.06	0.03	9139	0.0681
1997	0.1	0.03	9139	0.0012
1998	0.05	0.03	9139	0.09
noHS[a]	−0.07	0.02	63	0.0003

[a]noHS, proportion of total population that did not complete high school. SE, standard error

high school in the parish (ALHS) (p =0.0085) (Table 4). The number of a physicians in a parish (PHYS), the number of physicians per capita in a parish (PHYSC), and the percent of persons who had a digital rectal exam (DRE) in the last two years in a region (containing three or more parishes) were not associated with prostate cancer incidence in black males (p >0.20).

Covariate adjustment controlling for both structured and unstructured variation. For this analysis, HGLM was used with age and time-adjusted expected values, including a covariance structure with weights based on distances between parish centroids. Among white males, increased SIRs were associated with decreasing percent of persons who did not complete high school in the parish (ALHS) (p =0.01). Among black men, increased SIRs were no longer significantly associated with either the percent of persons who did not complete high school in the parish (ALHS) (p =0.30) or the proportion of males of aged 85 or older (among those aged 30 years and older) in a parish (P85) (p =0.33).

Cluster analysis adjusted for covariates. The results from SaTScan™ identified clusters of parishes with significant high and low relative risks (Figure 5). Among white males, clusters of increased relative risk were located in the Baton Rouge area (Cluster 3, RR=1.26, p =0.001) and Shreveport area (Cluster 1, RR=1.11, p =0.001). Clusters of decreased relative risk were located in the southeastern coastal area (Cluster 4, RR=0.80, p =0.001), and central Louisiana (Cluster 2, RR=0.89, p =0.001). Among black males, clusters of increased relative risk were located in the Baton Rouge area (Cluster 2, RR=1.25, p =0.001) and the entire northern region (RR=1.12, p =0.001) (not shown in Figure 5B). Clusters of decreased relative risk were located in central/southwestern area (Cluster 1, RR=0.84, p =0.001) and the southeastern area (Cluster 3, RR=0.89, p =0.001).

Discussion

This study illustrates a six-part spatial statistical methodological approach to analyze prostate cancer spatial variation within Louisiana at the parish level, and to provide insights into temporal trends and the effect of covariates. Prior studies of regional variation in prostate cancer incidence rates in Louisiana have not used this approach.[34]

Spatio-Temporal Patterns and Association

The spatial patterns of direct standardized rates, SIRs, and smoothed SIRs show consistently higher rates and SIRs among black males than white males (Figures

Table 4. Hierarchical general linear modeling regression coefficients, black males

Variable	Estimate	SE	DF	*p*-value
Intercept	−4.33	0.09	61	<0.0001
Age				
85+	Reference			
30–34	−8.46	0.71	9119	<0.0001
35–39	−8.44	0.71	9119	<0.0001
40–44	−5.37	0.17	9119	<0.0001
45–49	−3.76	0.09	9119	<0.0001
50–54	−2.78	0.07	9119	<0.0001
55–59	−1.71	0.05	9119	<0.0001
60–64	−1.18	0.05	9119	<0.0001
65–69	−0.58	0.04	9119	<0.0001
70–74	−0.31	0.04	9119	<0.0001
75–74	−0.15	0.04	9119	0.0008
80–84	−0.05	0.05	9119	0.29
Year of diagnosis				
1999	Reference			
1988	−0.43	0.06	9119	<0.0001
1989	−0.36	0.05	9119	<0.0001
1990	−0.28	0.05	9119	<0.0001
1991	−0.18	0.05	9119	0.0006
1992	−0.07	0.05	9119	0.163
1993	−0.01	0.05	9119	0.766
1994	0.02	0.05	9119	0.6636
1995	−0.02	0.05	9119	0.6586
1996	−0.03	0.05	9119	0.5303
1997	0.03	0.05	9119	0.5413
1998	−0.02	0.05	9119	0.6304
1999	0			
PR>85 years[a]	16.07	3.54	63	<0.0001
NoHS[b]	−0.08	0.03	63	0.0069

[a]PR>85 years, proportion greater than 85 years of age among those older than 30 years.
[b]noHS, proportion of total population that did not complete high school.

1–3). Among white males, the predominant temporal pattern is the rapid increase in prostate cancer incidence rates/ratios between the first (1988–1990) and second (1991–1993) time periods, reflecting the introduction of PSA screening in Louisiana during the late 1980s and early 1990s. The higher rates along the northern Louisiana–Arkansas border and the Baton Rouge area are consistent with the PSA screening campaigns that began earlier in these areas. Among black males, higher incidence rates are observed in the same areas, peaking during the second (1991–1993) and third (1994–1996) time periods. This trend reflects a lag in PSA screening among black males despite their higher risk for prostate cancer. In the last time period (1997–1998), relatively low rates and SIRs persisted in some areas, primarily central rural Louisiana for whites and central Louisiana and south coastal parishes for blacks. The global Moran statistics indicated significant autocorrelation was present, and the high–high (low–low) clusters (Figure 4) from the LISA cluster map support these observations.

Although maps (Figures 1–4) were helpful in exploring spatio-temporal patterns, caution is needed in interpretation because the number of males in an racial-age group in a parish (AGE) may not be adequately controlled and other covariates or autocorrelation may be responsible for the spatial patterns observed. Hierarchical models were applied to identify covariates that might explain the spatio-temporal patterns. The number of males in a race-specific age group in a parish (AGE), the year of diagnosis group (YEARGRP), the percent of persons in a parish who did not complete high school (ALHS), and the proportion of males of aged 85 or older among those aged 30 years and older in a parish (P85) (black only) were significant when only unstructured random errors were included. Models not including a spatial autocorrelation term when fit to data with spatial autocorrelation may lead to overestimation of *p*-values.[35] In this case, Moran's I statistic suggested spatially correlated error terms in these data, and when this term was included the significance level of the percent of persons in a parish who did not complete high school (ALHS) for black men was reduced from $p < 0.01$ to $p = 0.30$.

The SaTScan™ results showed clusters of parishes with significantly higher and lower SIRs after controlling for covariates. This spatial pattern shows the residual or remaining geographic variation after removing the effect of the number of males in a

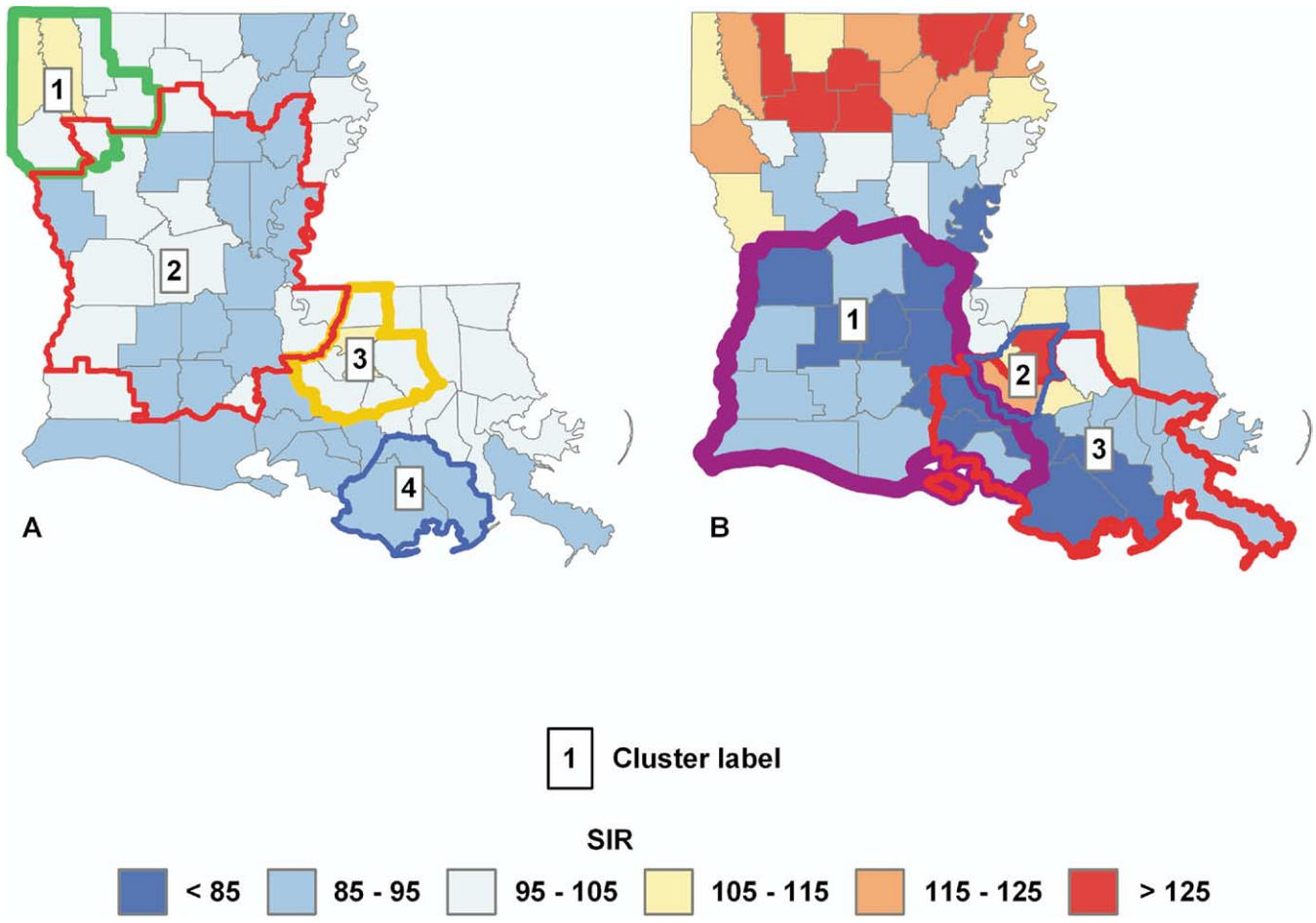

Figure 5. Clusters of parishes identified by SaTScan™ using observed and expected values aggregated over four time periods in Louisiana. Expected cases are derived from a hierarchical generalized linear model including spatially structured and unstructured Poisson variation. (**A**) White males: controlling for single year of diagnosis; age group; and percent not completing high school. (**B**) Black males: controlling for single year of diagnosis, age group; proportion of males aged 85 years or older (among those at aged 30 years and older); and percent not completing high school. [1] indicates a primary cluster, and [2], [3], and [4] indicate secondary clusters in descending order of significance.

race-specific age group in a parish (AGE), the single year of diagnosis (YEAR), the proportion of males of aged 85 or older (among those aged 30 years and older) in a parish (P85), the percent of persons in a parish who did not complete high school (ALHS), and random unstructured and structured error (autocorrelation) terms. A potential question for future study would be the extent to which the residual spatial pattern might reflects the level of aggressiveness of PSA screening.

Other Cancer Applications

Although this article focused on prostate cancer for illustrative purposes, the methods also might be a useful starting point for cancer registry spatial analyses of other types of cancer.

For example, late-stage breast cancer incidence rates or SIRs could be mapped to identify areas where screening mammography should be targeted. A series of maps for different time periods using the same cut-points could be used to assess the impact of screening mammography on stage at diagnosis over time.

Similarly, hierarchical modeling and cluster analysis also might be useful as part of efforts to study the relationship between lung cancer and air pollution. Significant risk factors for lung cancer could be controlled such as county-level smoking rate, SES, and prevalence of high risk occupations. Adjusted SIRs could be mapped to identify "residual" significant spatial variation that may be associated with air pollution.

Technical Considerations

Direct versus indirect adjustment. Because cancer risk increases with age and the population's age distribution influences crude cancer rates, comparison of cancer rates among different populations or geographic areas must be age adjusted. Age standardization can be carried out by either direct or indirect methods. A subject of debate has been whether the direct or indirect method should be used. Examples of issues have included: what is the

purpose of the adjustment (e.g., is the purpose of the adjustment to compare disease rates between populations that have different age–gender characteristics, or is the purpose of the adjustment to assess the need for resources to affect changes in the rates)[36]; does appropriate data exist to make valid estimates of disease rates for age–gender subgroups of the population for small areas[36]; and whether the two methods give equivalent results.[36–38] The advantage of direct adjustment method is that rates are more comparable,[37] but age-adjusted rates can be unstable for areas with small populations. Indirect adjustment is a better approach for areas with small numerators and denominators because the SIRs can be estimated with more precision and are more likely to be robust. In this study, both methods of age-adjustment yielded similar results, consistent with simulation studies.[37] If the methods produce conflicting results, examination of the confidence intervals of rates and variance of the ratios is necessary to determine if the discrepancies are a result of small numbers.

Map smoothing and cluster analysis. Map smoothing provides reliable disease rates and ratios by aggregating data over contiguous geographic units. In this process, true differences (clusters and outliers) in small areas may be removed. The selection of a specific smoothing method often depends on the number of geographic units and the variability of rates/ratios. The Bayesian method was chosen because it easily allowed for the inclusion of a spatially structured variation.

Kulldorff's spatial scan test has several advantages over other local cluster detection tests, namely, a formal likelihood test statistic, avoidance of multiple testing, and not restricting scanning for clusters of a pre-specified size, thereby avoiding pre-selection bias.[33,40] At the time of this study, the available version of SaTScan™ software used a circular window to define the potential cluster areas and thus might have had difficulty in correctly detecting noncircular clusters. In future studies, exploration of a flexibly shaped spatial scan statistic might be advantageous in an irregular shaped state such as Louisiana.[39]

Use of Bayes and HGLM models. The HGLM analysis with structured and unstructured covariance was repeated using Bayes method with a CAR model. The time trends and association with other covariates observed for HGLM and Bayes were similar for each race group. SaTScan™ identified the same clusters for both methods with only minor changes in small parishes. The choice of which of these methods to use is more likely to depend on the experience of the staff rather than any substantive statistical reason.

Bayesian analysis incorporates the observed data and prior information to estimate the distributions of unknown quantities of interest. In the Bayesian setting, the structured variability is defined using a conditional autoregressive function where the weights are based on adjacent neighbors. In contrast, the HGLM approach estimates the parameters via pseudo maximum likelihood methods. The HGLM approach was selected for several reasons: the software was familiar, no a priori information was required, convergence was rapid, and handling multiple covariates was relatively easy.

Conclusion

Tools and theory for spatio-temporal analyses are still in the relatively early stages of development. In the interim until research can identify consensus on an optimal approach, the multiple method approach illustrated in this article would seem to be a useful starting point for cancer registry analysis of spatio-temporal patterns.

The interpretation of the results of spatio-temporal patterns requires some caution. For example, the ecologic fallacy of applying aggregate data to individuals, the long latency of cancer, and the migration of the population may obscure or exaggerate the association between environmental exposures and cancer incidence. Further, failing to control for covariates and confounders may yield misleading results. For example, using the prostate cancer analysis in this article for illustrative purposes, a direct measure of PSA screening would have been extremely helpful. Unfortunately, parish-level PSA screening data were not available during the study period.

Despite these limitations, visual presentation of spatio-temporal variation can be an effective tool to communicate summary data to the general public. Cancer registry, cancer control program, and public health community should include staff with expertise in GIS and spatial analysis methods to facilitate the preparation, visualization, and interpretation of cancer data at the state level.

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