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A GEOGRAPHIC ANALYSIS OF PROSTATE CANCER MORTALITY IN THE UNITED STATES, 1970–89

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The recently published atlas of cancer mortality in the United States revealed that prostate cancer mortality rates were elevated among white men in the Northwest, the Rocky Mountain states, the north-central area, New England and the South Atlantic area, and among black men in the South Atlantic area. Here we determine whether the elevated regional rates were statistically different from rates in the rest of the country and whether the pattern can be explained by selected regional characteristics. A spatial scan statistic was applied to county-based mortality data from 1970 through 1989 to identify geographic clusters of the elevated rates for prostate cancer. Five clusters of elevated mortality were detected in white men ($p < 0.005$) and 3 in black men ($p = 0.0001–0.056$). For white men, the primary cluster was in the northwestern quadrant, followed by clusters in New England, the eastern part of the north-central area, the mid-Atlantic states and the South Atlantic area, whereas for black men the primary cluster was in the South Atlantic area, followed by clusters in Alabama and the eastern part of the north-central area. Further analyses of these clusters revealed several significant subclusters ($p < 0.05$). None of the selected demographic and socioeconomic factors, separately or collectively, accounted for the primary clusters in the U.S. white and black populations. The patterns observed could not be attributed to selected demographic or socioeconomic characteristics but should provide leads for further study into the risk factors and the medical or reporting practices that may contribute to geographic variation in mortality from prostate cancer.

Key words: *prostate cancer; cluster analysis; geographic; demography; epidemiology*

Prostate cancer mortality rates have varied about 12-fold internationally, with recent rates being highest among U.S. blacks and lowest in Hong Kong; rates among whites in Europe and North America have varied about 2-fold.[1] U.S. black men ranked first and white men eighth in world-wide prostate cancer mortality rates,[2] with 30,200 estimated deaths in the United States during 2002.[3] Over time the mortality rate among whites has increased from 20.3 per 100,000 person-years in 1973 to 24.7 in 1991 and then decreased to 19.6 in 1998.[4] By comparison, the mortality rate among blacks rose from 39.5 per 100,000 person-years in 1973 to 56.2 in 1993 and then declined to 48.7 in 1998.

The recently published atlas of cancer mortality in the United States, covering the periods 1950–69 and 1970–94, revealed intriguing geographic patterns for prostate cancer.[5] Age-adjusted rates by state economic area tended to be higher in the Northwest, Rocky Mountain, north-central, New England, and South Atlantic areas among whites (Fig. 1, upper panel) and in the South Atlantic area among blacks (Fig. 1, lower panel). Similar patterns were noted in previous surveys of prostate cancer mortality in the United States,[6–8] particularly the north-south gradient among whites. Our study was designed to test whether the geographic variation in prostate cancer mortality forms clusters of elevated rates that are statistically significantly different from the national rate, and whether the variations can be explained by selected demographic and socioeconomic factors.

MATERIAL AND METHODS

We obtained population estimates (U.S. Bureau of Census) and the number of prostate cancer deaths (National Center for Health Statistics) for each county in the contiguous United States for the years 1970–89 by 5-year age groups, for white and black men. We excluded 31 deaths for which the corresponding age-specific population values were zero. We limited our analysis to the period before 1990, in an effort to assess geographic patterns before the mortality rates started to decline and to exclude the influence, if any, of screening on the death rates. The geographic central position (centroid) of each county was specified using measures of latitude and longitude as established by the U.S. Bureau of the Census (1991).[9]

We used a spatial scan statistic[10,11] to detect and evaluate the statistical significance of geographical clusters. The number of deaths in each county was modeled as a Poisson distribution. Under the null hypothesis, the expected number of deaths is proportional to the indirectly age-adjusted population at risk. An infinite number of circles is superimposed on the map, using the county centroid as their center. The radii of the circles are set to vary continuously from zero to a maximum where at most 50% of the total population at risk is included. The data for an entire county are included if the centroid is included. Thus, any given circle contains different sets of neighboring counties, and each circle represents a potential cluster of prostate cancer mortality.

For each circle, the likelihood is calculated for observing the number of deaths occurring within that circle. The circle with the maximum likelihood is the most likely (i.e., primary) cluster, that is, the cluster that is least likely to have occurred by chance alone. The distribution of the maximum likelihood under the null hypothesis is evaluated using Monte Carlo hypothesis testing, and its simulated p-value is obtained by comparing the maximum likelihood from the real data set with the maximum number generated in random replications (9999) of the data under the null hypothesis. In addition to the primary cluster, the spatial scan statistic identifies secondary clusters, and their statistical significance is evaluated by comparing their likelihoods with the maximum likelihood of the primary cluster in the random data sets, giving a slightly conservative test for secondary clusters.[10]

A feature of the spatial scan statistic is that if the null hypothesis is rejected, then we can pinpoint the location of the cluster causing the rejection, and the null hypothesis would be rejected irrespective of the geographic distribution of deaths outside the circle. If there is more than 1 significant cluster, then each cluster is able to reject the null hypothesis on its own strength. The likelihood for a circle will often change very little when adding or removing a single county. Although it is possible to pinpoint the general

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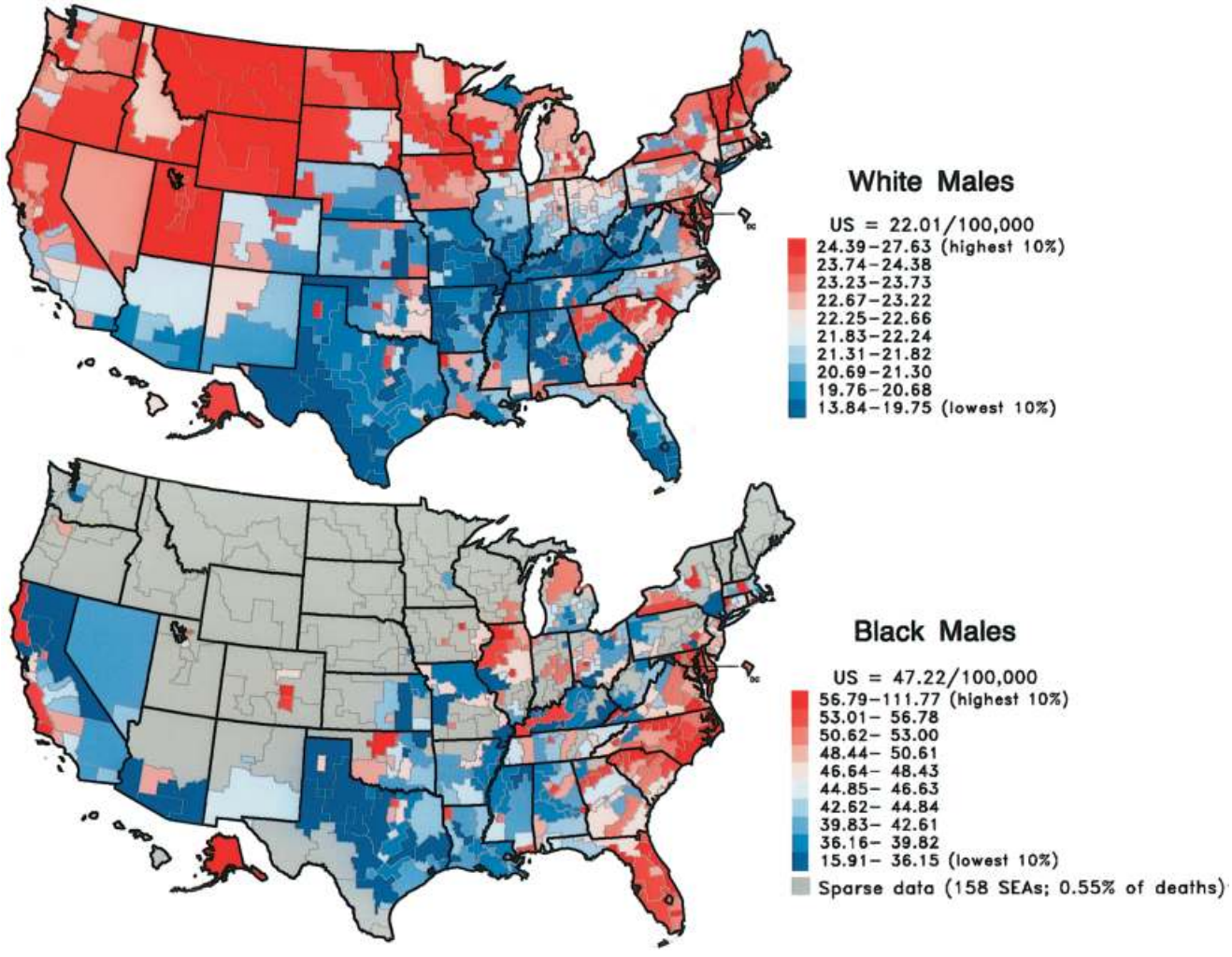

FIGURE 1 – Prostate cancer mortality rates among whites (upper panel) and blacks (lower panel) by state economic area, 1970–94.

TABLE 1 – OBSERVED AND EXPECTED NUMBERS OF PROSTATE CANCER DEATHS, MORTALITY RATES, AND RELATIVE RISKS BY CLUSTER FOR WHITE MALES

Approximate locations	Number of deaths		Rate[1]	RR[2]	*p*-value[3]
	Observed	Expected			
(United States)	382,204	382,204	20.2	1.000	—
Most likely cluster					
A: Northwest quadrant	69,421	65,221	21.5	1.064	0.0001
Secondary clusters					
B: New England	46,510	44,091	21.3	1.055	0.0001
C: Maryland, Virginia, Pennsylvania	13,484	12,554	21.7	1.074	0.0001
D: Michigan, Ohio, Indiana, Illinois	66,339	64,509	20.8	1.028	0.0001
E: South Carolina, North Carolina	3,956	3,629	22.0	1.090	0.0027
Subclusters					
A1: Montana, North Dakota, Wyoming	7,644	6,667	23.2	1.147	0.0001
A2: Minnesota, Iowa, Wisconsin	8,362	7,424	22.8	1.126	0.0001
A3: California, Oregon	7,833	7,223	21.9	1.084	0.0001
A4: Washington, Oregon	7,336	6,866	21.6	1.068	0.0005
A5: Utah, Nevada, Colorado, Arizona	2,470	2,231	22.4	1.107	0.0170
A6: Iowa, Missouri	519	415	25.3	1.249	0.0235
B1: Vermont, New Hampshire, Maine	5,430	4,822	22.8	1.126	0.0001
B2: Massachusetts, Rhode Island	3,159	2,774	23.0	1.139	0.0001
B3: Massachusetts, Connecticut	5,448	5,093	21.6	1.070	0.0194
C1: Maryland, Delaware	4,931	4,419	22.6	1.116	0.0001
D1: Kentucky, Ohio, Indiana	2,410	2,123	23.0	1.135	0.0001
D2: Wisconsin	7,562	7,112	21.5	1.063	0.0033

[1]Mortality rates are per 100,000 person-years and are indirectly adjusted using the age-specific national rate for the whole study period.–[2]Risk relative to the national rate.–[3]Probability that a cluster of this magnitude will be observed by chance.

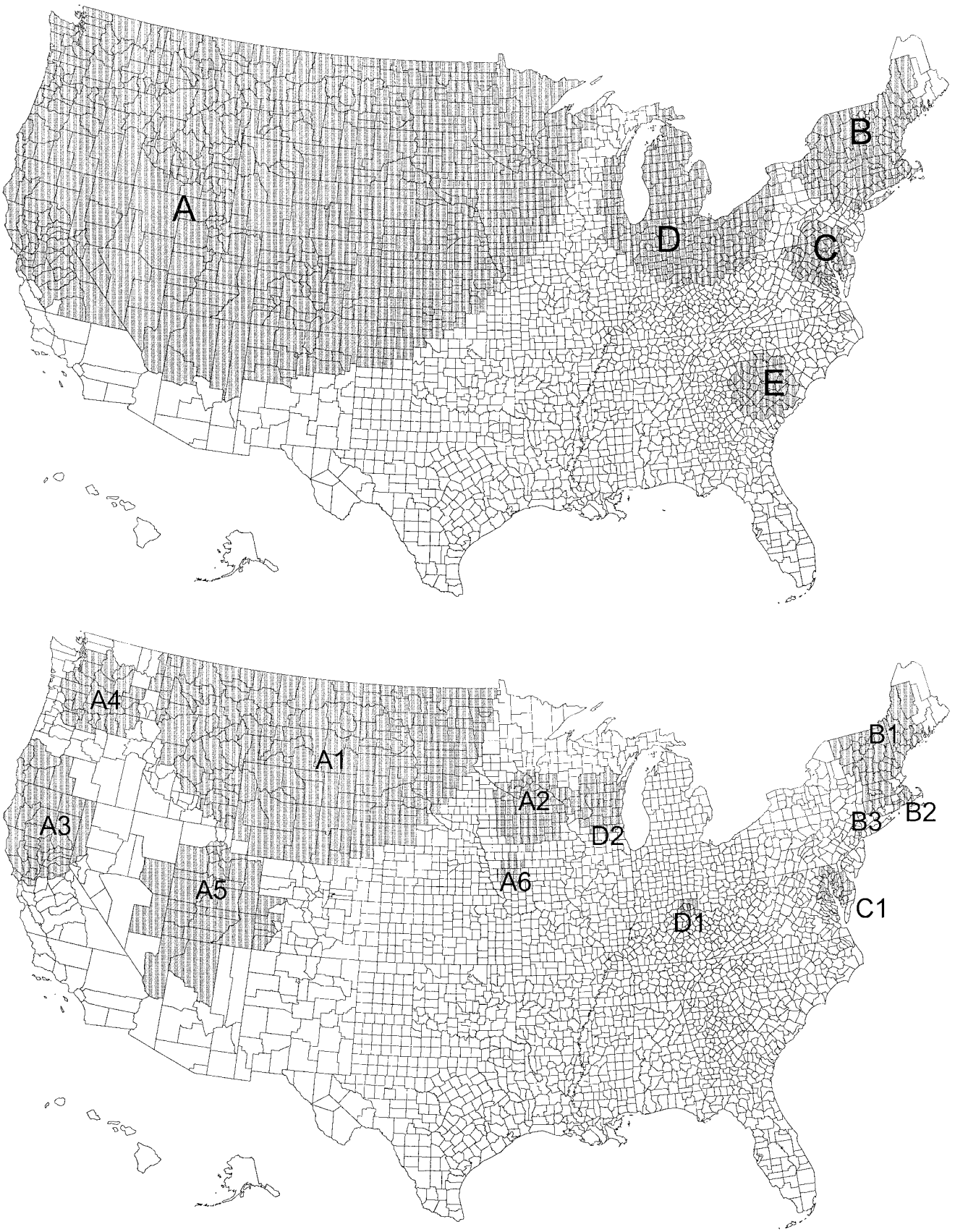

FIGURE 2 – The most likely cluster (A) and 4 secondary clusters (B–E) of prostate cancer mortality for 1970–89 among whites (upper panel); subclusters of prostate cancer mortality among whites (lower panel).

location of a cluster, we cannot determine its exact boundaries. We do not report all secondary clusters, only those that do not overlap with another reported cluster of higher likelihood. Sometimes there are smaller subsets of a larger cluster, such that the subsets themselves are capable of rejecting the null hypothesis on their own strength. As these subclusters often provide important information at a finer scale, they are reported in a second round of analyses.

In addition to the indirectly age-adjusted analyses, we also conducted analyses adjusted for Hispanic ethnicity among whites and for education and agricultural employment among both blacks and whites. Mortality data specific for white Hispanic men were not available for the entire study period 1970–89. In recent years, white Hispanic men had a risk about 30% lower than white non-Hispanic men for mortality from prostate cancer.[4] Assuming this risk to be equal for each age group, we multiplied the age-adjusted population at risk for each county with $1 - 0.3 \times H/100$, where H is the 1980 percent Hispanic population in that particular county, in order to obtain an age- and Hispanic-adjusted population at risk. Since we are using a Poisson model, it is only the relative size of the population at risk in the various counties that matters. Education and agricultural employment were adjusted for at the county level, since reliable estimates are lacking concerning the relative mortality risks for individuals categorized according to those variables. Each county was classified as having a median education level of <9 years of schooling, 9–11 years, 12 years, and >12 years based on the average for 1970 and 1980 among persons aged 25 years and over.[12] The percentages of the county population age 16 and older that were employed in agriculture (including fisheries) were averaged for 1970 and 1980 and then categorized by quartiles. The spatial analyses were then done as before, but where the null hypothesis allows the risk to be different in the different strata, and where a detected cluster of counties reflects more observed deaths in those counties than what would be expected if they had the same risk as the average of their respective strata.

RESULTS

For white men, we detected 5 statistically significant geographic clusters with elevated risks of prostate cancer mortality (Table I, Fig. 2A). The primary cluster was in the northwestern quadrant of the country, with a relative risk of 1.06 ($p = 0.0001$). Secondary clusters among whites were located in New England, the eastern part of the north-central area, the mid-Atlantic states and the South Atlantic area, with relative risks ranging from 1.03 to 1.09. Further analyses of these clusters resulted in the identification of several significant subclusters (Fig. 2B). The relative risks for these subclusters ranged from 1.06 in Wisconsin to 1.25 in Iowa (Table I).

For black men, we detected 3 statistically significant clusters (Table II, Fig. 3A). The primary cluster was in the South Atlantic area, with a relative risk of 1.11 ($p = 0.0001$). Secondary clusters were found in Alabama and in the eastern part of the north-central area, with relative risks of 1.16 and 1.08, respectively. Further analysis uncovered 5 statistically significant subclusters within the South Atlantic cluster, with relative risks ranging from 1.14 to 1.32 (Fig. 3B).

In general, adjustment (in addition to age) for Hispanic ethnicity, median years of schooling and percent employed in agriculture slightly changed the characteristics of the primary clusters. For whites, individual adjustments for Hispanic ethnicity and percent employed in agriculture and simultaneous adjustments for all variables slightly increased the size of the northwestern quadrant cluster, whereas adjustments for median years of schooling decreased its size. The center of the cluster shifted slightly during adjustments, except for agriculture. For practical purposes, the primary cluster remained the same and highly significant, and the slight change in position should be viewed in light of the fact that we can only specify the general location of a cluster and not its exact boundaries.

For blacks, individual or simultaneous adjustments for median years of schooling and percent employed in agriculture did not affect the characteristics of the South Atlantic cluster. The secondary cluster in the eastern part of the north-central area was the only 1 affected by adjustment; it disappeared among blacks when we individually adjusted for median years of schooling and percent employed in agriculture, and it became smaller and nonsignificant among whites when we adjusted for median years of schooling.

DISCUSSION

In a geographic analysis of prostate cancer mortality at the county level in the United States, we found several geographic areas with elevated relative risks ranging from 1.03 to 1.32. Due to the large population size and frequency of the disease, even a small excess in risk may have public health significance. For example, in the primary cluster among whites, located in the northwest quadrant of the country, there were 4,200 excess prostate cancer deaths during the time period 1970–89, or 210 excess deaths per year. Despite methodologic differences between studies, the modest regional variations we observed in prostate cancer mortality in the United States resemble the findings from a survey of prostate cancer incidence in Great Britain, 1975–1991.[13] In that study, prostate cancer risk showed geographic variation at a regional level, with incidence relative risks ranging from 0.83 to 1.2.

It is difficult to evaluate whether the geographic patterns of prostate cancer mortality are influenced by regional variation in diagnosis and reporting, including accuracy of death certifications. Since malignant neoplasms reported on death certificates are usually selected as the underlying cause of death,[14] regional differences in ascertainment would have to be substantial to account for

TABLE II – OBSERVED AND EXPECTED NUMBERS OF PROSTATE CANCER DEATHS, MORTALITY RATES, AND RELATIVE RISKS BY CLUSTER FOR BLACK MALES

Approximate locations	Number of deaths		Rate[1]	RR[2]	p-value[3]
	Observed	Expected			
(United States)	71,692	71,692	28.6	1.000	—
Most likely cluster					
A: South Atlantic	19,370	17,390	31.9	1.114	0.0001
Secondary clusters					
B: Alabama	1,198	1,032	33.3	1.161	0.0050
C: Ohio, Indiana, Michigan, Kentucky	3,715	3,451	30.8	1.077	0.0561
Subclusters					
A1: North Carolina, South Carolina	4,110	3,492	33.7	1.177	0.0001
A2: Florida, Georgia	3,803	3,230	33.7	1.177	0.0001
A3: Maryland, Virginia, Delaware	4,088	3,523	33.2	1.160	0.0001
A4: Georgia, North Carolina	2,543	2,228	32.7	1.142	0.0001
A5: Georgia	329	249	37.8	1.319	0.0200

[1]Mortality rates are per 100,000 person-years and are indirectly adjusted using the age-specific national rates for the whole study period.–[2]Risk relative to the national rate.–[3]Probability that a cluster of this magnitude will be observed by chance.

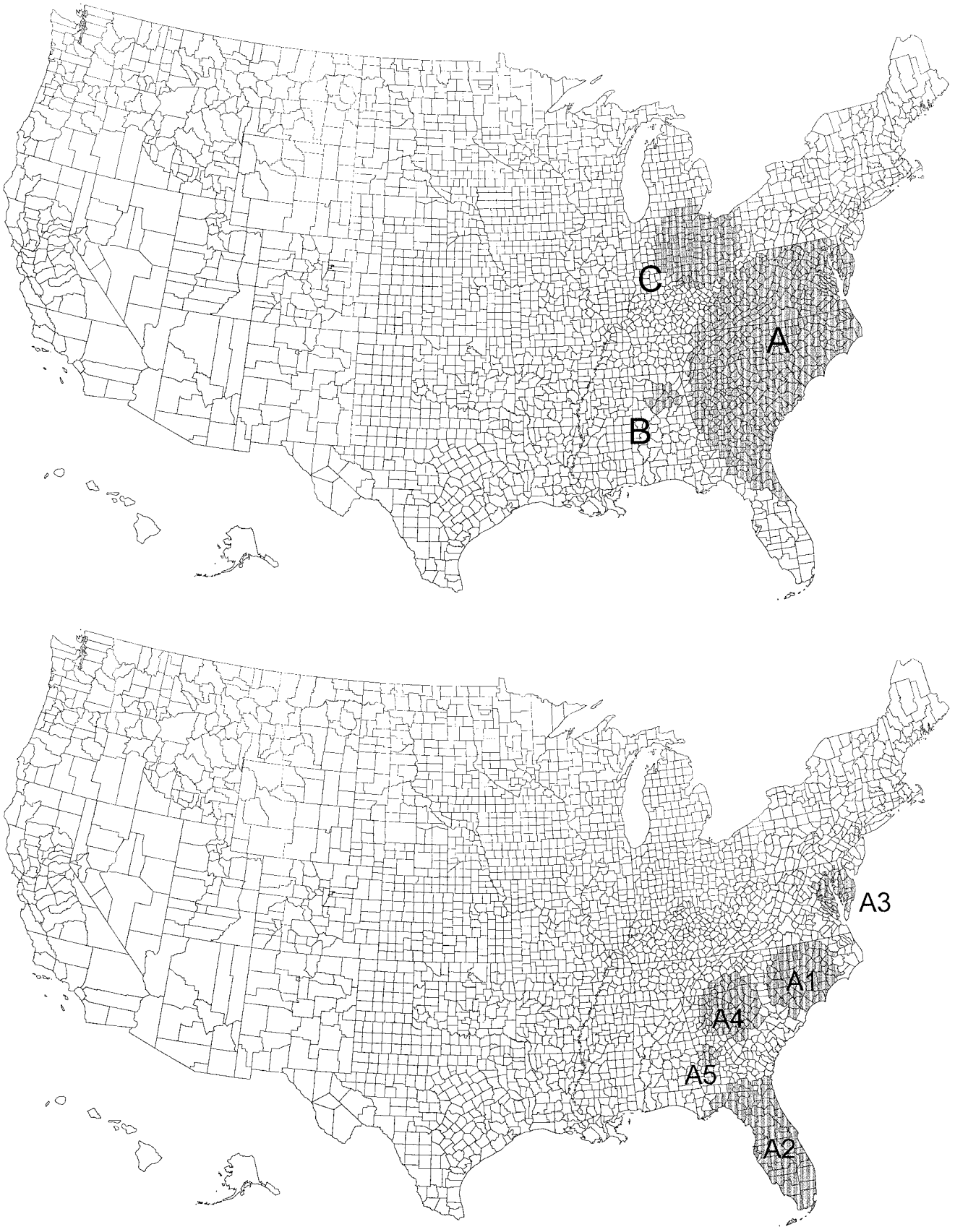

FIGURE 3 – The most likely cluster (A) and 2 secondary clusters (B, C) of prostate cancer mortality for 1970–89 among blacks (lower panel); subclusters of prostate cancer mortality among blacks (lower panel).

the variations in reported mortality across the United States. Nevertheless, increases in transurethral resection of the prostate (TURP),[15,16] radical prostatectomy[17] and testing for serum prostate-specific antigen (PSA)[18] have led to upward trends in prostate cancer incidence, resulting in increases in the recording of prevalent cases and/or occult lesions on death certificates.[19] The frequencies of TURP[20] and radical prostatectomy[17,20,21] have been shown to vary across the United States and thus may have contributed to the geographic patterns of prostate cancer mortality. Although PSA testing also varied geographically,[22] it became widespread only in the late 1980s and thus seems unlikely to have influenced the mortality patterns seen during 1970–89.

The only well-established risk factors for prostate cancer are age, ethnicity and family history of prostate cancer. Our analysis adjusted for age and considered whites and blacks separately, but lacked data on family history. In the United States, prostate cancer mortality rates for whites are about half the rates reported for blacks but more than twice those reported for Asians.[4] In the white population, Hispanic men have a 30% lower risk than non-Hispanic men for deaths due to prostate cancer. Since the Hispanic population is concentrated in the southern and western parts of the United States, this low-risk population may contribute to the north-south gradient of prostate cancer mortality among whites and to the formation of northern clusters. However, our statistical adjustment for Hispanic ethnicity did not alter the excess risk among whites in the northwest quadrant or in any of the secondary clusters.

The reasons for the geographic patterns of prostate cancer mortality are unclear. A number of studies have reported a slightly elevated risk of prostate cancer among farmers,[23–27] possibly due to pesticide exposures[28,29] or dietary intake of animal fat.[26] When our geographic analyses adjusted for the percent of adults employed in farming, there was no evidence that agricultural exposures explained the excess risk in the northwest quadrant among whites or in the South Atlantic area among blacks. However, such exposures may have contributed to the excess risk in the north-central area among blacks.

Our analysis did not take into account other potential risk factors that may contribute to the geographic variation in prostate cancer mortality, such as the prevalence of sexually transmitted diseases (STDs)[30,31] or the levels of environmental selenium.[32] STDs have been associated with increased risk for prostate cancer among U.S. whites and blacks,[30,31] and the population-attributable risk may be greater in blacks due to the higher prevalence of STDs in this population.[33] We lacked race-specific county-level data on STDs to correlate with prostate cancer mortality, but it is noteworthy that the southeastern part of the country has the highest prevalence of STDs[33]along with elevated prostate cancer mortality.

A protective effect of selenium was suggested by Schrauzer *et al.*,[34] who found a significant inverse correlation between selenium in food and prostate cancer mortality based on data from 27 countries. Subsequently, in a nested case-control study design, a reduced risk of advanced prostate cancer was found among American men with higher prediagnostic levels of selenium in toenails.[35] Furthermore, in a double-blind cancer prevention trial, a daily supplement of 200 μg of selenium for 4 years was associated with a 63% reduction in the development of prostate cancer.[36] In the United States, however, the area in the northwest quadrant with the highest prostate cancer mortality among whites appeared to have adequate levels of selenium, as measured in forage crops.[32]

Our geographic analysis is based on mortality data, which may reflect not only the prevalence of risk factors but also survival rates after diagnosis. Stage at diagnosis[4] and access to treatment, as reflected by socioeconomic status.[37,38] strongly influence survival; however, prostate cancer mortality rates among U.S. whites were slightly elevated in counties with higher socioeconomic levels[6] as measured by educational attainment, a correlation we also found in the most recent mortality data (not shown). In our analysis, adjustment for educational attainment did not influence the elevated prostate cancer risk among whites in the northwest quadrant or among blacks in the South Atlantic area, but it attenuated the excess risk in the eastern part of the north-central area among blacks and whites.

In summary, our study revealed that the geographic variation in prostate cancer mortality across the United States reflects significantly elevated rates in contiguous high-risk areas and cannot be explained by selected socioeconomic and demographic factors, individually or collectively. Further studies targeted to specific regions of the country should help to identify the risk factors and the medical or reporting practices that may contribute to the geographic patterns in prostate cancer mortality.

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