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A Spatiotemporal Analysis of Invasive Cervical Cancer Incidence in the State of Maryland Between 2003–2012

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Abstract

Purpose—Invasive cervical cancer (ICC) rates have tremendously declined in the United States, yet new cases consistently occur in Maryland and throughout the United States. We hypothesized that although rates have generally declined, this decline is uneven across counties and over time.

Methods—Space-time cluster detection analysis to evaluate clusters of ICC incidence at the county level within Maryland between 2003 and 2012.

Results—The most likely cluster was a cluster of low incidence, which included 6 counties in eastern Maryland for the period 2009–2012. A secondary cluster of low rates, comprising 2 metropolitan counties in northern Maryland, was observed for the period 2009–2012.

Two of the 3 clusters of high ICC rates occurred 2009–2012 in the large metropolitan area of Baltimore City and another cluster in Frederick County, in rural western Maryland. The third cluster of high rates was observed 2005–2008, in western Maryland.

Conclusion—In recent periods, some Maryland counties have experienced anomalous high or low ICC incidence. Clusters of high incidence are not explained by differences in screening rates and may be due to failures in follow-up care for cervical abnormalities that need to be investigated. Clusters of low incidence may represent areas of successful ICC control.

Keywords

space-time cluster detection; spatial epidemiology; cervical cancer; cancer surveillance; SaTScan

INTRODUCTION

Beginning in the 1950s, rates of invasive cervical cancer (ICC) in the United States (US) have steadily declined due to the introduction and use of Pap screening as a screening test

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for early detection of ICC and its associated precancerous lesions [1, 2]. In spite of this decline, data from the Centers for Disease Control indicate that 12,360 new ICC cases are diagnosed annually [3]. Further, about 4,000 ICC associated deaths are recorded annually [3] and in 2010 alone about 100,000 years of life were lost to ICC [4, 5].

Human papilloma virus (HPV) infection is the necessary cause for cervical cancer [6]; however, the continued presence of ICC in the US is in part due to underlying inequalities in access to preventive and treatment services [2, 7]. Nationally, there are known disparities in ICC incidence, with racial minorities, low income and rural populations having the highest disease burden [8–12]. For example, ICC incidence rate among older black women is twice the rate among white women of the same age even after accounting for differences in hysterectomy rates [13].

Current ICC incidence in the state of Maryland reflects national rates, and similar to national trends, every year there continues to be women diagnosed with ICC and some ICC deaths recorded in Maryland [14]. Therefore given the availability of effective screening tests (like Pap tests and HPV testing) and treatment, which makes ICC highly preventable and treatable, the state of Maryland identified ICC as one of its seven high priority cancers for targeted action [15, 16]. As part of its ongoing efforts to address ICC, the state offers low-income, uninsured, and underserved women free ICC screening, diagnosis and treatment services through the Centers for Disease Control's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) [17]. However, even with the NBCCEDP program, prevalence of Pap screening remains lower among some key populations including uninsured women and women without a primary care provider [18]. In addition, research in Maryland suggests that compared to white women, black women have significantly higher ICC incidence and mortality rates [15]. In addition, black women are more likely to present with more advanced cases of ICC and are less likely to receive appropriate treatment given the stage of disease [14].

Previous Maryland state cancer reports have described both overall ICC incidence across Maryland and by the 24 counties, including Baltimore City, within the state [15, 19]. These reports however, did not examine the space-time variation in ICC incidence across Maryland. Further, they did not assess the combined effect of contextual factors at the county level, (such as socioeconomic characteristics, overall health status, screening rates, and racial composition) and how these factors might influence observed variations in ICC.

Spatial epidemiology presents a formal way to separate signal from noise in examinations of trends in incidence across geographic units and over time while accounting for relevant factors that might influence any observed variation [20–23]. Tools from the field of spatial epidemiology, such as the cluster detection approach, allow for the objective identification and visualization of geographic areas of anomalous cancer incidence in space and time [24]. Additionally, areas of significantly high or low cancer incidence identified using spatial epidemiology can inform efficient redistribution of cancer prevention and control efforts [5, 25].

Using a space-time model, a previous examination of variation in ICC incidence by counties in the United States reported elevated rates in counties with a low prevalence of cervical cancer screening and a higher incidence for some racial minority groups including non-Hispanic blacks, American Indians and Hispanic women [4]. This study however, was conducted for a relative short period (2000–2003) and provided limited information about specific areas of elevated rates. In addition, it did not assess the significance of the observed increase in ICC incidence in some geographic areas, including Maryland. Thus, this current study assessed variation in ICC incidence by counties in the state of Maryland over a 10-year period. We hypothesized that although national and Maryland state rates have generally declined, after accounting for differences in relevant county characteristics, over time some counties have experienced an ICC incidence that is either significantly higher or lower than expected.

METHODS

Data and Study Population

Data on ICC cases diagnosed between January 2003 and December 2012 were obtained from the Maryland Cancer Registry. For each case, data from the Cancer Registry included information on county of residence at diagnosis, age at diagnosis, country of birth (or state for those born in the US) and marital status. Additional information on type of reporting source (medical provider/health facility, lab only and death certificate), race, grade, metastasis, insurance status (uninsured, private, public and other) and diagnostic confirmation (histology, cytology and clinical) was provided. The analysis was restricted to ICC cases 18 years or older and resident in the state of Maryland at the time of diagnosis. Cases without available information on their county of residence at the time of diagnosis (n=9) were excluded from all county level analyses.

State and county population data as well as racial composition were obtained from the 2010 census and used as denominator for all incidence rate calculations. In addition, annual median household incomes by county were obtained from the Census Bureau's Small Area Income and Population Estimates (<https://www.census.gov/did/www/saipe/data/index.html>) [26]. Other county characteristics were obtained from the Maryland Behavioral Risk Factor Surveillance System (BRFSS) [27]. For each county, BRFSS data included information on prevalence of obesity and current smoking as well as percentage of females screened for cervical cancer within the last 3 years. All BRFSS data were obtained biennially (2004, 2006, 2008, 2010 and 2012) and all estimates of county covariates were assumed to be the same and lagged for years (2003, 2005, 2007, 2009 and 2011) in which data was not collected.

Descriptive Statistics

Characteristics of cases diagnosed within the study period were described using median values and associated interquartile range (IQR) values for continuous variables and percentages for categorical variables. The average annual crude incidence rates of ICC by county were calculated and choropleth maps of average annual crude incidence rates developed in ArcGIS[28] for the entire 10-year.

Space-Time Cluster Detection Analyses

A space-time cluster detection analysis evaluates the anomalous incidence of disease across both geographic area and over time. This type of cluster detection analysis relies on a cylindrical window the height of which is correlated with time and the circumference with space [29–31]. The study utilized retrospective space-time cluster detection analyses to identify areas of both high and low ICC incidence in Maryland from 2003–2012. The cluster detection analyses were conducted in SaTScan (www.satscan.org) using county of residence at the time of diagnosis, as the geographic unit of aggregation. Clusters included areas of both hot and cold spots of disease incidence, which were respectively defined as areas with either higher or lower incidence rates of disease than expected compared to rates in the rest of the state [31, 32].

Both the initial and final space-time cluster detection analyses were age adjusted using the 2010 female population of Maryland as reference standard. Adjustments in the SaTScan cluster detection algorithm serves to rule out clusters that would appear solely due to the adjusting variables. The final fully adjusted cluster detection analysis was further adjusted for prevalence of obesity, current smoking, minority (defined as non-white race and/or Hispanic ethnicity), percentage up to date on their cervical cancer screening (measured as Pap test within past 3 years) and median household income within each county.

Given the limited ability of SaTScan to adjust for variables of a continuous nature [31, 33, 34], separate Poisson regression analyses for adjusted ICC incidence were performed stratified by year in STATA14 [35]. The fitted or predicted mean of the Poisson regression model represents the expected number of cases per county and year adjusted for the included regression model covariates. These Poisson regression expected counts were imported back into SaTScan for the adjusted cluster detection analyses to search and identify clusters not already explained by the clustering of these adjusting variables. All cluster detection analyses were conducted using a circular buffer defined from each county centroid location and extending out to only consider clusters (collection of contiguous counties), which combined are within 50% of the total statewide population at risk. Further, for the cluster detection analysis ICC incidence was calculated over two-year periods (2003–2004, 2005–2006, 2007–2008, 2009–2010 and 2011–2012) in order to ensure enough statistical power. Space-time clusters were assessed based on relative risk (RR) estimates which compared the ICC risk within each cluster using the observed and expected ICC case count to the ICC risk at the state level [29, 31, 32]. The statistical significance of identified clusters were assessed using Monte Carlo simulations within SaTScan at a p-value 0.05 [29, 31, 32]. To visualize the results, identified significant clusters were mapped within ArcGIS [28].

RESULTS

There were 2,172 women diagnosed with ICC in Maryland between 2003–2012. At diagnosis most of the cases (46.7%) were 40–59 years old, with a smaller proportion of women below the age of 30 (4.6%) or 70 years or older (15.8%, Table 1). A sizeable proportion of cases were born in the US (42.2%), many of whom were born in Maryland (44.8%, 411/917). Fifty-eight percent of cases were white and 34.5% were black. At diagnosis, most cases had some type of insurance (77.2%), had grade III or IV cancers

(28.9%) and no metastasis (64.9%, Table 1). Most of the cases were either married or had domestic partners (37.6%) while the remainder were separated or divorced (13.9%), widowed (11.5%) or had never been married (27.2%, Table 1).

The average annual crude incidence rate of ICC in Maryland over the 10-year period assessed, was 7.3 per 100,000 and this rate varied across counties (Supplemental Figure 1). For this period, some counties including Baltimore City, Kent and Allegany had overall average annual crude rates that were double (~12–15 per 100,000) the crude state rate. Other counties including Dorchester and Talbot had crude rates as low as 4 per 100,000 for the 10-year period assessed (Supplemental Figure 1).

This geographic variation in rates was further confirmed in the space-time cluster detection analysis, showed significant space-time clusters of both higher and lower than expected rates of ICC incidence for some counties in Maryland (Figure 1 & 2). After adjusting for county age distribution, the overall average annual adjusted statewide ICC incidence rate was 9.7 per 100,000. The most likely cluster (i.e. the cluster least likely to be due to chance), in the initial age adjusted cluster detection analysis, was a cluster of higher than expected (RR= 1.82; 95% CI: 1.47, 2.25) ICC incidence identified in Baltimore City (Table 2). Baltimore City, is a large metropolitan area [36] that has a high proportion of low income communities (annual median household income in Baltimore City for the time period 2003–2006 ranged from \$29,162–\$35,834 [26] compared to a statewide annual median household income range of \$58,700–\$65,250 [37] for the same time period). The cluster in Baltimore City was observed for the time period 2003–2006, and had an average annual adjusted incidence rate of 17.1 per 100,000 (Table 2). Another significant cluster identified, was a cluster of lower than expected (RR=0.78; 95% CI: 0.64, 0.95) ICC incidence rates that emerged in a group of fringe metropolitan [36] higher income counties in south-eastern Maryland (Table 2, Figure 1). The annual median household income across these counties for the time period 2005–2008, ranged from \$63,005–\$101,867 [26] compared to a statewide annual median household income range of \$62,850 – \$69,550 [37] for the same time period. This cluster of low rate had an average annual age adjusted ICC incidence rate of 7.9 and was observed for the period 2005–2008.

After further adjustments for percent minority, percent screened for cervical cancer in the last 3-years, median household income, percent obese, and percent current smoker within each county, the overall average annual adjusted state ICC rate for the 10-year period was 9.2 per 100,000. In this fully adjusted analysis, two significant clusters of low and 3 significant clusters of high rates emerged over the time period assessed (p-value 0.05) (Figure 2). Both clusters of low ICC rates occurred in the more recent calendar years of the study and were in primarily rural and suburban counties of various sizes. The most likely cluster in this analysis was a cluster comprising six counties in eastern Maryland with a dramatically lower incidence of ICC than expected (adjusted relative risk (aRR)=0.08, 95% CI: 0.04, 0.16) for the period 2009–2012. Median income for these mostly nonmetropolitan counties ranged from \$39,630 - \$88,406 and had a Pap screening prevalence range of 81.6%–95.2% [18]. The other cluster of low rate (aRR= 0.41; 95% CI: 0.26, 0.65) was a secondary cluster, which comprised two large fringe metropolitan counties west and northwest of Baltimore, for the period 2009–2012. In this time period, counties in this

cluster, had a median income range of \$60,543–\$108,234 [26] and a screening prevalence range of 86.7%–92.2% [18]. Comparatively for this time period, 2009–2012, the statewide screening prevalence range was 82.1%–86.7% [18] and median income ranged from \$69,193 to \$71,122 [37].

The first significant cluster of high ICC rate ($aRR=2.52$; 95% CI: 1.40, 4.52), identified in the fully adjusted analysis, was observed for the period 2005–2008 in Allegany and Garrett counties, which are respectively small metropolitan and rural counties in Western Maryland. For this cluster, median income ranged from \$33,643 to \$43,496 and Pap screening prevalence ranged from 72.5% to 83.6% within the time period identified. In this time period, 2005–2008, prevalence of screening in Maryland ranged from 84.1% to 87.6% and median income ranged from \$62,850 to \$69,550.

Baltimore City remained a cluster of high rate ($aRR=1.74$, 95% CI: 1.39, 2.18) in the fully adjusted analysis, however unlike the initial cluster of high rate identified in the age and population size adjusted analysis, this cluster was for a more recent time period, 2009–2012. In Baltimore City, median income within this time period ranged from \$38,186 to \$39,077 and screening prevalence ranged from 82.0% to 84.9%. Another cluster of high rates ($aRR=2.47$, 95% CI: 1.44, 4.22) emerged in rural western Maryland in Frederick county for the period 2011–2012 (Table 2, Figure 2). For this time period, median income within this county ranged from \$77,872 to \$80,427 and Pap screening prevalence was 67.1%. The last cluster of high rate ($aRR=1.33$) identified in the adjusted analysis was observed in the suburban large fringe metropolitan county of Montgomery; however, this cluster was not statistically significant (95% CI: 0.90, 1.96) and was for the period 2003–2006.

DISCUSSION

In this retrospective space-time cluster detection analysis of ICC incidence in Maryland, most counties had consistently moderate ICC incidence across the time period examined. However, several hotspots of high and low incidence were also detected. These findings show that although overall statewide ICC incidence is generally low, there are areas, even in the most recent time period, that experienced an irregularly high incidence of ICC. Clusters of low ICC incidence identified provide evidence of the impact of state and county level efforts to address ICC in Maryland and suggest that ongoing prevention and control efforts have been highly successful in specific areas of the state. Understanding these remaining areas of anomalous ICC incidence can help to help prioritize additional interventions or outreach that may be most impactful. In addition, the findings we present for this study can be used in the future as benchmark to assess the progress made towards addressing ICC in Maryland, over time.

The ICC clusters identified in Maryland by our study are not explained by the age distribution, average screening rates in the county, health status (smoking and obesity), median household income and health insurance coverage within counties contained in the clusters identified. Of course, individual level impact of these factors remains, especially as most ICC cases are known to be underscreened or never screened [38–40]. Our adjustment for average county screening suggests the clusters observed are not due to availability of

screening in the area. When untreated cervical abnormalities, especially those of a high grade will eventually progress to invasive disease. Therefore, these identified clusters may be due to other factors associated with differences in the timeliness and appropriateness of follow-up care for cervical abnormalities detected as part of routine screening [41–43]. These other factors that we did not have data to examine may include the proportion of women who seek follow-up testing after an abnormal Pap test result [41], average time to follow-up testing and treatment after an initial abnormal result [41, 42] as well as the proportion of women living with HIV [44, 45] within each county. In addition, we cannot rule out the potential for residual confounding even for the factors adjusted for in our analysis.

The average annual age adjusted incidence of 9.7 per 100,000 observed in our study for Maryland is comparable to the reported national rate of 7.7 per 100,000 within the same time period [46]. In addition, within our study period (2003–2012), the national average age annual adjusted ICC incidence decreased significantly at a rate of 1.3% per a year [46]. In spite of the decrease in national rates and a comparable national and Maryland state average annual ICC rate of 7.3 per 100,000, the findings of our cluster detection analysis support our study hypothesis. They indicate that even in recent time periods, the burden of ICC is uneven across smaller geographic units and that there are still some counties experiencing an anomalously high ICC incidence. Thus, identifying and investigating these units can further accelerate the decline of ICC incidence at the national and state levels.

Our analysis of variation in cervical cancer incidence among counties in Maryland has several strengths and to our knowledge this is one of the first studies to assess the space-time variation of ICC incidence at the county level. Our study included 10 years of data to allow for assessments of temporal variation, and incorporated information on county characteristics from different data sources to assess if there are significant space-time clusters that are not explained by the county characteristics. The detection of significant clusters of both high and low ICC incidence provides additional data that can be used to prioritize ICC needs at the county level and ensure effective ICC prevention and control.

This study also has some limitations. Our evaluation of a space-time variation in ICC incidence was conducted at the county level and could not explore potential heterogeneity in incidence rates that may be present at smaller geographic units, such as census tracts, within each county [20, 47]. However, given the relatively low number of ICC cases, conducting our analysis at the county allowed for an adequate sample size within each geographic unit [20]. A second limitation is that these county based findings and resulting inferences made about ICC risk at the county level may not hold true at smaller geographic units or for individuals within those counties [20, 48].

In conclusion, the observed clusters of high and low ICC incidence provide evidence of a significantly non-uniform ICC incidence across counties in Maryland within the 10-year period assessed. The clusters of lower than expected rates identified provide evidence supporting the impact of state and local efforts to address ICC. While the clusters of higher than expected rates suggest that in spite of the progress made over time, some counties have

seen an increased ICC incidence rate, which should be monitored and considered for targeted interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Age-adjusted map of significant ($p < 0.05$) space-time clusters of high (red) and low (green) invasive cervical cancer incidence rates by county in Maryland, 2003–2012. The average annual age-adjusted Maryland state incidence rate for this period was 9.7 per 100,000.

Figure 2.

Adjusted map of significant ($p < 0.05$) space-time clusters of high and low invasive cervical cancer incidence rates by county in Maryland, 2003–2012. Adjusted for age distribution, median household income, cervical cancer screening rates, prevalence of smoking and obesity within each county. The average annual adjusted Maryland state incidence rate for this period was 9.2 per 100,000.

Table 1

Characteristics at diagnosis of 2172 invasive cervical cancer cases 18 years or older, diagnosed in Maryland between 2003 to 2012

Descriptor	n (%)	Maryland Population ^a (%)
Age at diagnosis, years		
29	99 (4.6)	20.4
30–39	402 (18.5)	16.6
40–49	576 (26.5)	19.7
50–59	439 (20.2)	18.5
60–69	314 (14.5)	12.5
70	342 (15.7)	12.4
Birth location		
United States	917 (42.2)	84.8
Maryland	411 (18.9)	
DC, VA, PA	144 (6.6)	
North East (other than PA) ^b	69 (3.2)	
Midwest ^c	25 (1.2)	
West coast ^d	7 (0.3)	
South (other than DC, VA, MD) ^e	98 (4.5)	
Other ^f / U.S. region unknown	163 (7.5)	
Outside United States	150 (6.9)	15.2
Africa	28 (1.3)	
Europe	9 (0.4)	
South America & Caribbean	65 (3.0)	
Asia & Middle East	27 (1.2)	
Other	21 (1.0)	
Unknown	1105 (50.9)	
Race		
Black	750 (34.5)	29.9
White	1254 (57.7)	60.3
Other	143 (6.6)	9.8
Unknown	35 (1.6)	
Marital status		
Never married	591 (27.2)	31.8
Married/Domestic partner/Other	817 (37.6)	46.9
Separated/Divorced	262 (12.1)	11.9
Widowed	216 (9.9)	9.4
Unknown	286 (13.2)	
Insurance status		
Uninsured	131 (6.0)	

Descriptor	n (%)	Maryland Population ^a (%)
Private Insurance	748 (34.4)	
Public Insurance	586 (27.0)	
Other	345 (15.9)	
Unknown	362 (16.7)	
Type of reporting source		
Medical provider/Health facility	1976 (91.0)	
Lab only	155 (7.1)	
Death certificate	41 (1.9)	
Grade		
I	213 (9.8)	
II	537 (24.7)	
III/IV	627 (28.9)	
Unknown	795 (36.6)	
Metastasis		
No	1410 (64.9)	
Yes	201 (9.3)	
Unknown	561 (25.8)	
Diagnostic confirmation		
Histology	1952 (89.9)	
Cytology	76 (3.5)	
Clinical	12 (0.6)	
Unknown	132 (6.1)	

^a2010 female Maryland population who were 18 years or older

^bNortheast: Connecticut Delaware Massachusetts Maine New Hampshire New Jersey New York Rhode Island Vermont [47]

^cMidwest: Illinois Indianapolis Kansas Michigan Missouri Nebraska Ohio Wisconsin

^dWest coast: California Colorado Hawaii Washington [47]

^eSouth: Alabama Arkansas Florida Georgia Kentucky Louisiana Mississippi North Carolina South Carolina Oklahoma Tennessee Texas West Virginia [47]

^fOthers: Guam

Table 2
Space-time clusters of invasive cervical cancer incidence rates by county in the state of Maryland, 2003–2012.

Space-Time Clusters	Average annual adjusted rates per 100,00	Standardized Incidence Ratio	Population Size	Relative Risk	95% Confidence Interval	p-value	Time period, years
Age-Adjusted^a							
Most likely cluster:							
Baltimore City	17.10	1.76	251,347	1.82	(1.47, 2.25)	<0.001	2003–2006
Secondary Clusters:							
• Montgomery, Prince George's, Howard, Charles, Anne Arundel	7.90	0.82	1,082,960	0.78	(0.64, 0.95)	0.014	2005–2008
• Caroline, Talbot and Queen Anne's	1.00	0.11	46,146	0.11	(0.003, 3.92)	0.228	2011–2012
Fully Adjusted^b							
Most likely cluster:							
Dorchester, Talbot, Caroline, Wicomico, Calvert and Queen Anne's	0.80	0.08	129,755	0.08	(0.04, 0.16)	<0.001	2009–2012
Secondary Clusters:							
• Baltimore City	15.50	1.68	251,347	1.74	(1.39, 2.18)	<0.001	2009–2012
• Carroll and Howard	3.80	0.42	169,883	0.41	(0.26, 0.65)	<0.001	2009–2012
• Frederick	22.40	2.44	86,870	2.47	(1.44, 4.22)	0.001	2011–2012
• Allegany and Garrett	22.90	2.50	39,689	2.52	(1.40, 4.52)	0.002	2005–2008
• Montgomery	11.90	1.30	382,099	1.33	(0.90, 1.96)	0.150	2003–2006

^aRelative risk estimates compare the ICC risk within each cluster using the observed and expected ICC case count to the ICC risk at the state level

^bAverage annual age-adjusted statewide ICC incidence for the 10-year period, 2003–2012, was 9.7 per 100,000 and the analysis was adjusted for the age distribution within each county.

^cAverage annual adjusted statewide ICC incidence for the 10-year period, 2003–2012, was 9.2 per 100,000 and the analysis adjusted for age distribution, percent minority, percent screened for cervical cancer in the last 3-years, median household income, prevalence of obesity and smoking within each county.