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Predictors of Late Stage Cervical Cancer Diagnoses and Disparities in the U.S. (A Closer Look at the Interactions Between Characteristics of Access, Women & Place)

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ABSTRACT

PREDICTORS OF LATE STAGE CERVICAL CANCER DIAGNOSES AND DISPARITIES IN THE U.S.

(A CLOSER LOOK AT THE INTERACTIONS BETWEEN CHARACTERISTICS OF ACCESS, WOMEN & PLACE)

By

YAMISHA S. RUTHERFORD

AUGUST 29, 2019

Background: Approximately 51% of women with cervical cancer (CVC) are diagnosed at a late stage (regional or distant), an outcome associated with increased morbidity and mortality. African American, and Hispanic women, and women residing in specific geographic regions of the (US) are among those most heavily burdened by late stage CVC. The cause(s) of these disparities are multifaceted and not well understood. However, the most significant predictor of late stage CVC diagnosis and disparities is current screening, which is largely impacted by access to care. Thus, the goal of this study was to identify access-related predictors of late stage CVC and develop a comprehensive understanding of *where* and *why* racial and geographic disparities in late stage CVC occur. **Methods:** This three-part study examined primary CVC cases diagnosed between the years of 2005-2014, from the United States Cancer Statistics (USCS) database. The final sample included 120,325 CVC cases within 43 states and their 2,357 constituent counties. First, Empirical Bayes LISA clustering methods were applied to identify clusters of counties considered to be high risk for late stage CVC “hotspots” during two 5-year time periods (pre- and post-2010). Second, a series of T-tests were conducted to determine whether various contextual and compositional factors were significantly different in hotspots versus other places. Third, two Generalized Linear Mixed Models (GzLMM), using data from person and county levels, were estimated to identify predictors of late stage CVC diagnosis and racial or ethnic disparities among women with CVC in the US. Lastly, a General Linear Mixed Model (GLMM) using data from county- and state –levels was estimated to

examine predictors of higher proportions of late stage CVC among counties. **Results:** Primary care physician shortage areas, Planned Parenthood (PPH) clinics, area-level poverty rates, area-level uninsured rates, percent of immigrants from other countries, state CVC screening mandates and prevalence of self-insured employer health plans were all statistically significant predictors of access to care associated with late stage CVC diagnoses and geographic disparities. We also found that PPH clinics play an important role in reducing the odds of late stage CVC among Hispanic women with CVC. **Conclusion:** Access to CVC screening plays a significant role in the etiological pathway to late stage CVC diagnoses and disparities. Given that significant access barriers occurred at various ecological and geographical levels, it is recommend that future research and intervention efforts begin to focus on multilevel and/or spatial approaches. Without further exploration of the factors impacting late stage CVC diagnoses, CVC mortality rates will remain high and at a disproportionately higher rate for women in various geographical areas and among African American and Hispanic women.

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APPROVAL PAGE

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Author's Statement Page

August 29, 2019

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Yamisha S. Rutherford

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Abbreviations and Acronyms

ACA Affordable Care Act
CDC Centers for Disease Control
CHC Community Health Centers
CVCC Cervical Cancer
EB Empirical Bayes
FIPS Federal Information Processing Standard
FQHC Federally Qualified Health Centers
GIS Geographic Information Systems
HPSA Health Professional Shortage Area
HPV Human Papillomavirus
LISA Local Indicators of Spatial Association
MLM Multilevel Model
NP Nurse Practitioner
PCP Primary Care Physicians
PPH Planned Parenthood
RDC Research Data Center
SEER Surveillance, Epidemiology and End Results
SES Socioeconomic Status
USCS United States Cancer Statistics

Chapter One

Introduction

Early detection and treatment of cervical cancer (CVC) can significantly reduce the probability of cancer mortality.¹ Despite the advantage of early detection, preventive screening is significantly underutilized² and 51% of women with CVC are diagnosed at a late stage (regional or distant).³ Late stage CVC diagnosis rates are disproportionate across various populations, with minority women and women in specific geographic regions reporting significantly higher rates.⁴⁻⁸ The cause(s) of these disparities are multifaceted and not well understood. However, the most significant predictor of stage at CVC diagnosis is current screening (i.e. having a Pap smear within the past three years) , which is a known proxy for access to care.⁹⁻¹¹

Several studies in the current literature suggest that the implementation of the Affordable Care Act (ACA) has helped to mitigate the issue of poor access to CVC screening by providing affordable insurance to more than 20 million individuals in the US.^{12,13} In addition, the ACA mandated that health insurance plans were required to cover CVC screening in full, with no cost-sharing. Although the ACA has made significant strides toward improving access to CVC screening,¹⁴⁻¹⁵ there are several factors and exclusions that reduce the potential for ACA mandates to have its intended effects.¹⁶⁻¹⁷ Thus, the ACA has fallen short of eliminating screening access barriers for all women.

These limitations along with the fact that significant disparities in stage at CVC diagnosis still exist, suggest the presence of additional factors influencing access to CVC screening and the pathways driving disparities in stage at CVC diagnosis. Thus, the purpose of this study is to contribute to this understudied body of literature by identifying access-related predictors of late stage CVC and developing a comprehensive understanding of *where* and *why* disparities in late stage CVC occur. Specifically, this study aims to apply unexplored model-based constructs and novel methodologies to determine whether racial and geographical disparities in late stage cervical cancer diagnosis exist (and persist) and how multilevel access barriers impact them. These multilevel access barriers include state Nurse Practitioner (NP) regulations, state cervical cancer screening mandates, PCP shortages, publicly funded health center density and the percent of the population in self-insured plans, all of which have never been explored in relation to stage

at CVC diagnosis or disparities. The ultimate goal of this study is to support progress toward eliminating disparities in late stage CVC diagnosis rates by pinpointing areas in greatest need of screening intervention, identifying significant access barriers and providing evidence for policy change and implementation.

The investigation of these disparities will begin in Chapter 1. Chapter 1 will begin with a literature review to describe background information on the topic of cervical cancer (CVC), late stage CVC disparities and the role of access to care. Secondly, this study will describe theoretical and methodological problems/gaps in the current literature as it relates to the topic and innovative solutions to these problems. We will then describe the purpose of the study and how we plan to apply those innovative solutions to carry out three research aims. The following sections will describe the theoretical underpinning and the significance of the study.

Literature Review

Cervical Cancer Epidemiology & Prevention

In previous years, cervical cancer was the second most common cancer among women. In 90% of cases cervical cancer is caused by the Human Papillomavirus (HPV), a commonly occurring sexual transmitted disease.¹⁸ Based on United States Cancer Statistics (USCS) data collected from 2010-2014, there were 46,848 women alive in the US who were diagnosed with CVC.¹⁹ More recent data on cervical cancer incidence suggests that there were 12,845 new cases of CVC in the US in 2015.¹⁹ Compared to the CVC incidence rate of 9.6 per 100,000 in 2000, the overall age-adjusted incidence rate was 1.9 per 100,000 women lower in 2015.¹⁹ This decline can be attributed to two methods of cervical cancer prevention and early detection i.e. HPV vaccination and Pap testing.²⁰⁻²¹ As of December 2014, there were three vaccines available in the US to prevent HPV infection, Cervarix (HPV2), Gardasil (HPV4) and Gardasil 9 (HPV9). According to the National Cancer Institute, the HPV vaccine can prevent up to 81% of new cervical cancer cases.²² In addition to the HPV vaccines, screening to detect and treat abnormal cervical cell changes (pre-cancers) before they potentially develop into cervical cancer (i.e. Pap testing) is also a well-known and available method for preventing cervical cancer. Due to early detection, cervical cancer has been found to be one of the most treatable cancers among all cancers.²⁰

Late Stage Cervical Cancer & Disparities

Despite the known effectiveness of Pap testing, 31% of women aged 18² and over had not been currently screened for cervical cancer and 51% of women in Surveillance, Epidemiology and End Results (SEER) states who had been tested were diagnosed at a late stage (regional or distant).³ Specifically, 36% of the CVC cases were diagnosed at regional stage where there is a regional lymph node metastasis and 15% at distant stage where there is a distant metastasis including peritoneal spread, involvement of supra-clavicular, mediastinal, or para-aortic lymph nodes, and spread to the bladder, lung, liver, or bone.^{3,23} Beyond the high incidence of late stage cervical cancer, it is even more alarming that the burden of late stage cervical cancers disproportionately affects some women more than others. Epidemiological surveillance indicates that unmarried²⁴ foreign born²⁵ and minority women⁴⁻⁸ have significantly higher odds of being diagnosed with late stage cervical cancer compared to their counterparts. Epidemiologic studies have also found that women in specific geographic regions and women over age 50⁴⁻⁸ have greater odds of late stage cervical cancer compared to others.⁸

Among these disparities, geographic and racial disparities have been most persistent across various populations in the US. According to an early time trends study, the odds of late stage cervical cancer among African American women increased over a 15 year time period (1976 - 1990).¹¹ A later 2009 analysis of SEER data reported that African Americans were diagnosed at more-advanced stages than Whites for all four cancers with widely recommended screening procedures, including cervical, breast, colorectal and prostate cancer.⁶ A 2011 MMWR also reported that the incidence of late stage cervical cancer was nearly two times as high among Hispanic compared to White women, 8.4 per 100,000 vs 4.9 per 100,000 respectively.⁸

Previous research further suggests that disparities in late stage CVC incidence exist between different geographic populations.^{4,9-11,26} In fact, there is scientific evidence that suggests that there is extreme variability in the rates of late stage CVC at both the census tract and state level. For example, a 2014 study found that there was significant variability in stage at CVC diagnosis among 4,388 census tracts in the state of Texas (TX).²⁶ Major findings from this study indicate that clusters with statistically significantly increased risk for late stage CVC were located in the Western tip of TX, Southern TX, the Bryan/College State area and central Houston.²⁶ In regards to the state level, evidence suggests that late stage cervical cancer incidence rates were highest in

Arkansas, the District of Columbia, Illinois, Kentucky, Louisiana, Mississippi, Nevada, New Mexico, and Oklahoma.⁸

Factors Impacting Late Stage Cervical Cancer

The current literature assessing predictors of late stage cervical cancer incidence identifies socioeconomic status (SES), insurance coverage, insurance type, and current screening as factors associated with late stage cervical cancer.²⁷⁻³² A bivariate analysis conducted in early 2000 using Florida state cancer registry data found that patients with lower income levels had a greater likelihood of late stage cervical cancer compared to those with higher income levels (52% vs 33.3%; P.04).²⁷ A later study published in 2014, using 1995-2008 data from the Texas Cancer Registry found that the odds of advanced stage cervical cancer among patients in census tracts with the lowest SES were 1.54 times the odds of advanced stage cervical cancer among those in census tracts with the highest SES.²⁶

A more recent 2016 multivariate analysis using 2007-2011 SEER data found that patients who were uninsured were 1.21-2.03 times more likely to be diagnosed with distant site cervical cancer compared to those who had insurance coverage.²⁸ Another study using the National Cancer Database suggests that the relative risk of late stage cervical cancer diagnosis among uninsured patients is 1.44 times the risk of late stage cervical cancer diagnosis among those with insurance coverage.²⁹ This study also found that the relative risk of late stage cervical cancer diagnosis among those enrolled in Medicaid is 1.37 times the risk of late stage cervical cancer diagnosis among those that were privately insured.²⁹ Similarly, research using California Registry data collected between 1996-1999 also found that the odds of late stage cervical cancer among those enrolled in Medicaid insurance was 2.8 times the odds of late stage cervical cancer among those not enrolled in Medicaid insurance.³⁰

Finally, a 2015 study using data from the National Breast and Cervical Cancer Early Detection Program found that those who were rarely or never screened were 3.59 times more likely to be diagnosed with late stage cervical cancer compared to those who had been screened within that past 5 years.³¹ Another more recent 2018 study among cases reported by the Outpatient Obstetrics and Gynecology clinic also found that the adjusted odds of late stage cervical cancer

diagnosis among those without a history of previous screening was 3.91 times the odds of late stage cervical cancer diagnosis among those who had a history of previous screening.³²

The Role of Access in CVC Screening

Research suggests that the most significant predictor of late stage diagnosis is current screening, which is largely impacted by access to care.⁹⁻¹¹ Access is defined as “the timely use of personal health services to achieve the best health outcomes.”³³ Health care access has also been defined as “the opportunity or ease with which consumers or communities are able to use appropriate services in proportion to their needs.”³⁴ It can further be defined by three constructs: availability, accessibility and affordability.³⁵⁻³⁶ This experience of access has been unequal across various individuals and places in the United States.³⁶ In fact, access to care is often determined by one’s race, ethnicity, socioeconomic status, age, sex, disability status, sexual orientation, gender identity, and residential location.³⁷ Research suggests that individuals facing the greatest barriers to obtaining basic health care services report negative health outcomes at a disproportionately higher rate.³⁸

According to the literature there a number of personal and structural barriers associated with inadequate access to care and lower CVC screening rates in the US Several studies suggest that recent immigration status and poor language proficiency are barriers to CVC screening among Hispanic populations.³⁹⁻⁴⁰ A 2017 multivariate analysis of predictors of barriers to CVC screening among low income and uninsured women enrolled in the Texas Cancer Screening, Training, Education and Prevention Program found that Hispanic women were 4.72 times more likely to report language barriers to CVC screening, compared to Whites.⁴¹ The literature also suggests that living in rural geographical locations is also a barrier to CVC screening. Specifically, women in rural areas and economically deprived non-rural communities are less likely to be screened for CVC and report lower screening rates compared to women in urban and suburban areas with higher incomes.³⁹ Another 2014 survey study investigating rural populations and CVC screening also found that 71% of rural Appalachian respondents reported “not being able to use public transportation to get to medical appointment” as a barrier to screening.⁴² A 2016 review of the literature describing CVC screening barriers among minority women also found that inadequate knowledge of CVC screening and provider relationships were both barriers preventing adequate screening rates among African American and Hispanic women.⁴³ Similarly,

a survey study published in 2016 also found inadequate knowledge to be a significant predictor of not receiving a Pap test⁴⁴ Specifically, regression analysis found that the odds of Pap testing among women with knowledge regarding the test was 1.63 times the odds of testing among those didn't have knowledge regarding Pap smears.⁴⁴

The literature also suggests that cost, affordability and usual source of care play important roles in access to CVC screening. In fact, an early 2003 study examining access barriers to preventative services using data from the Medical Expenditure Panel Survey found that women ages 21-64 who were uninsured and without a usual source of care were less likely to receive a Pap test.⁴⁵ Specifically, women who had a primary care provider were 2.06 times more likely to have a Pap test compared to women who had no usual source of care.⁴⁵ This study also reported that women with private HMO insurance were 3.95 times more likely to have a Pap test compared to women with no health insurance.⁴⁵ This study further concluded that differences in access to care measures were the drivers of the disproportionately lower receipt of Pap testing among minority women compared to White women.⁴⁵

Another study published in 2003 aiming to identify the relationship between access and Pap smear screening practices among Latino women in California also found insurance and usual source of care to significantly influence screening.⁴⁶ Results of this study suggest that Latino women who were insured were twice as likely to have a Pap test compared to those that were not and Latino women that had a regular source of health care were 1.8 times more likely to have a Pap test compared to those that didn't have a usual source of care.⁴⁶ A 2007 systematic review of 17 studies focusing on factors inhibiting and promoting cervical cancer screening among African American and Hispanic women concluded that lack of health insurance, usual source of care and SES were significant determinants of screening.⁴⁷ Among the 17 studies, 41% reported lack of insurance as a barrier to cervical cancer screening, 41% reported lack of a usual source of care as a barrier and almost all of the studies reported that SES was a barrier to cervical cancer screening.⁴⁷ A later 2017 multivariate analysis of predictors of barriers to CVC screening among low income and uninsured women enrolled in the Texas Cancer Screening, Training, Education and Prevention Program also found that 61.6% of respondents reported cost as a barrier to Pap testing.⁴¹

Previous ecological studies have also found that similar compositional and contextual factors are associated with disproportionate CVC screening and late stage CVC rates among geographic areas.⁴⁸⁻⁵³ Among these factors are area level socioeconomic status (SES)^{26, 48} and community-level age, race and immigrant composition.^{26,49} Studies have also shown that contextual factors impacting access to care are associated with CVC screening and stage at diagnosis.^{26,50-52} Specifically, the literature suggests that health services resources in the community, travel time to the nearest screening facilities and availability of services in the community represent contextual access to care factors associated with CVC screening and stage at diagnosis.^{26,52-53}

The Affordable Care Act & Access to CVC Screening

The implementation of the Affordable Care Act (ACA) has helped to mitigate the effects of poor access to CVC screening by providing affordable insurance to more than 20 million individuals in the U.S beginning in 2014.¹³ In addition, the ACA mandated that all health insurance plans were required to cover CVC screening in full, with no copayment or out of pocket costs to insureds beginning in 2012. As a result, the ACA has been found to be associated with increased CVC screening rates and early stage diagnoses.¹⁴⁻¹⁵ In 2016 a study reported that the ACA was associated with a 21.2% increase in early stage (stage I) cervical cancer diagnoses among cancer patients aged 19-25 years.¹⁴ A later 2017 systematic review also found that the ACA had a significant impact on cancer screening, including Pap tests, among 14 studies.¹⁵

Although the ACA has made significant strides toward improving access to CVC screening, it has not eliminated access barriers for all women. Following the implementation of the ACA there were still 44.4 million individuals left uninsured and thus potentially facing issues regarding affordability of care.⁵⁴ Furthermore, due to expanded insurance coverage provided by the ACA, the need for primary care physicians (PCP) is expected to increase to as many as 49,300 PCPs by year 2030.⁵⁵ This presents an issue of availability of care for several women, including those with insurance, as the US is already experiencing a climate of primary care physician shortage.

Further, although health insurance plans that were in place prior to the passing of the ACA were allowed time to come into compliance with ACA provisions before being permanently excluded, exclusions and loopholes were widespread.¹⁶⁻¹⁷ One such loophole allowed ‘grandfathered’

plans in states with no prior mandate for CVC screening to be exempt from the ACA mandated coverage of CVC screening.¹⁷ For a limited time period, individuals in ‘grandfathered’ self-insured plans were also exempt from many of the ACA provisions; a population that accounts more than 50% of persons with employer-sponsored health insurance.⁵⁶ Together these exclusions reduce the potential for ACA mandates to fully achieve their intended effects. These factors together with the persistence of significant disparities in CVC screening and stage at diagnosis, suggest the presence of unexplored and interconnected forces influencing access to CVC screening and pathways to late stage CVC diagnosis.

Problem Statement: Limitations in Literature

The source(s) of geographic and racial disparities in late stage cervical cancer incidence are multifaceted and not well understood. However, there is a well-documented link between inadequate access to care and health disparities.¹¹ In fact, inadequate access to essential health care services was listed as one of the most important determinants of health disparities as early as 1991.⁵⁷ While several studies have helped to advance our understanding of disparities in stage at CVC diagnosis and their relationship with access to care, the majority of the studies in the literature are outdated, include a small sample of the US population, and present notable limitations in their modeling approach.

We believe late stage CVC diagnosis rates and disparities are predicted by interactions among people and characteristics of their contextual environments which include varying dimensions of access to care. Thus, to properly model the etiological pathways to these outcomes we must consider the influence of the multiple constructs of access to care, the multiple levels in which these constructs exist and their spatial interactions with various compositional and contextual factors. This proposal aims to **shift current research or clinical paradigms** related to racial and geographical disparities in stage at cervical cancer diagnosis and the relationship between these disparities and various dimensions of access to health care by **utilizing data representing 43 of the 50 states** and **applying unexplored model-based constructs and novel methodologies and spatial perspectives**.

Unexplored Constructs of the Access Framework

Based on Aday and Andersen's access framework developed in 1974, access can be determined by assessing the influence of health policy on characteristics of the population at risk and characteristics of the health delivery system, which in turn influences both utilization of health services and customer satisfaction.⁵⁸ In this framework the health policy construct represents relevant health policy and health care reorganization programs aimed at improving access to health care.⁵⁸ The characteristic of the population at risk construct includes factors such as: age, sex, race, religion, family income, insurance coverage, rural/urban character, attitude toward medical care and perceived need for care.⁵⁸ The characteristics of the health delivery system construct includes: health personnel, structures in which health care and education are provided, the equipment and materials used in providing health services, volume and the distribution of medical resources in an area, travel time, waiting time, and how a patient is treated.⁵⁸ Finally, utilization of health services rates and customer satisfaction scores are referred to as outcome indicators representing an individual's passage through the system.⁵⁸

With guidance from this model, several studies in the literature have focused on one or more of these constructs to explain the issue of access in regards to some health service. In regards to the literature on access barriers influencing cervical cancer screening, there is a focus on only two of the three access dimensions mentioned in the access framework: characteristics of the population at risk or in very few cases characteristics of the health care delivery system. As described in the above literature review, access to screening is mainly associated with characteristics of the population at risk such as insurance status, SES, immigration status, language proficiency, rural/urban status and knowledge. This literature review also highlights a few characteristics of the health care delivery system that impact access to CVC screening such as the patient-provider relationship, transportation to the nearest provider and usual source of care.

However, there are additional access indicators underlying characteristics of health policy and the health care delivery system that likely influence current screening and stage at CVC diagnosis, yet they have been left unexplored. These factors include state policies regulating health professionals' ability to provide care and state insurance mandates requiring cervical cancer screening coverage, which represent factors underlying the health policy construct and primary care physician shortage and publically funded health center density, which represent

factors underlying the characteristics of the health delivery system construct. The distribution of each of these factors varies from place to place and their individual and interacting effects could potentially explain the persistent racial and geographical disparities in late stage cervical cancer incidence.

Primary Care Physician Shortages & Underserved Populations

Over time data has consistently demonstrated an unmet need of primary care physicians in the US. According to the Association of American Medical Colleges (AAMC), there was an estimated 91.7 primary care physicians per 100,000 people in the US in 2016.⁵⁹ This translates to a total supply of approximately 296,353 primary care physicians.⁵⁹ Considering the current supply, there were still 7,176 designated primary care health professional shortage areas (areas with ≤ 1 primary care physician per 3,500 people) in the US in 2017.⁶⁰ Current HRSA reports project that this shortage will worsen as the population grows and as expanded insurance coverage provisions of the Affordable Care Act take effect.⁵⁵ In fact, the PCP shortage is expected to increase to a range between 14,800 and 49,300 primary care physicians by year 2030.⁵⁵

The primary care physician shortage is of grave public health significance as leaving individuals without readily available care can impact a wide range of health outcomes. Research suggests that for every additional PCP per 10,000 people there is a 5.3% decrease in all-cause mortality per year.⁶¹ Research further suggests that the physician shortage is a key determinant of disparities in access to care. With over 100 million Americans living in a defined geographic area with a shortage of primary care health physicians (i.e. medically underserved)⁶², these individuals report a lower quality of health services and are less likely to receive routine medical procedures, including screening.⁶³ In fact, compared to women living in areas of higher physician density (500 or more office-based primary care physicians per 100,000), women who live in areas of lower physician density (<100 office-based primary care physicians per 100,000 women) were significantly less likely to receive a Pap test in the past 3 years.⁶⁴⁻⁶⁵

Nurse Practitioner Regulations

Although many incentives have been proposed to increase the number of primary care physicians, one of the most plausible solutions to the PCP shortage is the use of nurse

practitioners. Nurse practitioners are advanced practice nurses that receive training and enter the health care system in less time and have been shown to provide quality at lower costs per visit compared to their physician colleagues.⁶⁶ A number of studies and systematic reviews have shown that NPs score higher on measures such as patient follow up, time spent in consultations, and provision of screening, assessment, and counseling services, compared to physicians.⁶⁷ According to the American Academy of Nurse Practitioners there are approximately 140,000 NPs in the US.⁶⁸ With over 50% of the NP workforce practicing in primary care settings,⁶⁹ NPs are among the top health professionals providing primary care services in family planning clinics.⁷⁰ Compared to physicians, nurse practitioners have also been found to be the majority provider type in rural and underserved populations.⁷¹ Overall, the addition of NPs has not only increased overall access to health care⁷² but it has been associated with reaching unscreened and under-screened women and those women lost to follow-up.⁶⁸

Despite the known benefits of using NPs to address the access barriers associated with the existing physician shortage, there are several barriers these providers face in practicing to the full scope of their training. Among these barriers are state-based regulations limiting NPs' scope of practice. While some states allow NPs full independent scope of practice (evaluate, diagnose, treat, and prescribe under the exclusive licensure authority of the state board of nursing), others impose restrictions on NP practice, including supervision, delegation, team management by a physician or restrictions in at least one element of practice.⁷³ Recent data indicates that 22 states and the District of Columbia allow NPs full practice and 29 states impose restriction on their practice.⁷³ Many argue that complying to restrictive scope of practice laws could take time from both NPs and their supervising physicians⁷⁴ and limit the supply of health services.⁷⁵ Several organizations including the Institute of Medicine recommend removing these restrictions as they believe "optimal utilization of NPs could increase patients' access to timely high-quality, cost-effective, patient-centered care."⁷⁶⁻⁷⁷ In support of their claims, research indicates that states with full or less restrictive NP scope of practice laws are associated with increased office visits⁶⁹ and better access to quality care.⁷⁸

Community Health Centers & Publicly-Funded Clinics

Community health centers (CHC) were developed with the specific goal of providing high quality and comprehensive primary care to medically underserved populations, regardless of

their ability to pay.⁷⁹⁻⁸⁰ Both CHC and other publicly- funded health clinics provide free or low-cost services through a number of publicly-funded programs such as the Title X national family planning and Medicaid programs.⁷⁹ Grantee sites include federally qualified health centers (FQHC), planned parenthood affiliates, public health departments, hospitals and other health care providers. These sites provide a wide range of primary and preventive services, including cervical cancer screening, to individuals that are disproportionately uninsured, low income and racial and ethnic minority.⁸¹

Community health centers and other publicly-funded clinics are not evenly distributed across the US and many have been shut down due to lack of government funding.⁸² Some states have as many as 176 community health centers while others have a few as four.⁷⁹ Community health centers are essential to public health as they have been found to play a critical role in expanding access to care and reducing health disparities among their patient population of nearly 27 million.⁷⁹ In regards to cervical cancer, Title X-funded centers alone (including both CHC and publicly-funded clinics) were responsible for providing affordable CVC screening to more than 743,000 female clients across 3,900 Title X-funded health clinics in 2015.⁸¹ Data also suggests that community health centers, irrespective of public funding source, have been successful in expanding access to CVC screening and reducing related health disparities among their socioeconomically and racially diverse patient populations. In fact, health centers have provided 4% more Pap smear services over the last 3 years compared to other health providers, 85% vs 81% respectively.⁷⁹ Data also suggests that 92% of Hispanic women in need of Pap testing at health centers received these services compared to only 69% of Hispanic women in need of these services nationally actually received them.⁷⁹ Similarly, 89% of African American women in need of Pap test at health centers actually received these services compared to only 75% of African American women in need of these services nationally who actually received them.⁷⁹

State CVC Screening Insurance Mandates & Self Insured Plans

Since the early 1960s, requirements regarding coverage provisions of private health insurance policies have largely fallen under the jurisdiction of state governments.⁸³ Mandated state insurance coverage requirements were established in efforts to promote public health and improve access and treatment for people with specific diseases, including cancer. State cancer mandates now include requirements for screening, prevention and treatment.⁸³ In 2009, there

were approximately 25 cancer-related state insurance mandates.⁸³ Among those mandates, only two focused on cervical cancer, required coverage for cervical cancer screening and HPV vaccination. In this regard, there was significant variation across states. By 2009, 32 states and the District of Columbia required insurers to cover cervical cancer screening while 19 did not.⁸³

While state CVC screening mandates are now perhaps less important, following the implementation of new preventive services coverage provisions under the Affordable Care Act (ACA) from 2012-2014, there are still reasons to expect that they may be significant predictors of late stage CVC. First, they established a stronger baseline in states that adopted them prior to 2010 that was absent in other states. Thus, these states were poised to perform better than states who saw these requirements for the first time in 2010. Several other factors suggest the importance of state mandates in supporting access to healthcare.^{16, 83-86} For example, private health plans that existed prior to March 23, 2010 were considered ‘grandfathered plans’ and were exempt from required coverage for preventive services under the ACA, including CVC screening.¹⁶ Similarly, commercial health insurance inside and outside of the health insurance exchanges are exempt from the ‘no cost sharing’ feature of the preventive services provisions under the ACA when preventive services are not delivered by a network provider.⁸⁵ These types of loopholes reduced the potential for federal ACA mandates to achieve their intended effects on access to healthcare by exempting large portions of the insured population. Furthermore, a systematic review of studies investigating the ACA’s impact on cancer screening and diagnosis found that the impact on changes in screening in the general population was mixed.⁸⁶ Together these loopholes and findings suggest that state mandates may still play a significant role in access to healthcare post-ACA implementation in 2010.

In 2013, Miles-Richardson et al. examined the impact of state cervical cancer screening mandates on screening rates and racial disparities in screening rates among women in Georgia, North Carolina and South Carolina and found no significant effects.⁸⁷ However, a later 2017 study found that Pap test mandates increased past 2 year screening by 1.3 percent.⁸⁸ This study also indicated that the effects of these mandate on screening rates were significantly larger among Hispanic women.⁸⁸

We believe findings suggesting a relationship between CVC screening and state cancer-related insurance mandates have been inconsistent because there may be significant lags in effects, so

later studies may find larger effects. Also, studies have not considered important contingencies related to private sponsorship of self-insured plans, although these plans account for more than 50% of persons with employer-sponsored health insurance.⁸⁹ According to provisions under the Employee Retirement Income Security Act (ERISA), self-funded employer plans are exempt from most state insurance laws, including mandated benefits.¹⁶ However, self-funded plans established by public employers are not exempt from state insurance laws.¹⁶ Thus the effects of these mandates by states may depend upon how much of the self-insured population is in public or private plans.

Multilevel Modeling

In addition to the lack of available studies assessing the impact of factors representing the multiple constructs of access to care, current research investigating disparities in stage at CVC diagnosis and access to CVC screening has also failed to account for the simultaneous effect of factors occurring at multiple levels. In fact, several researchers have reported that despite efforts to change, many health disparity studies have continued to focus solely on individual level explanations and have failed to include explanations of the spatial processes and pathways to health outcomes.⁹⁰⁻⁹² This limited approach prevents researchers from understanding that many health outcomes such as access to screening and subsequent disparities in stage at diagnosis are influenced by complex and interacting social, environmental and behavioral processes that occur at varying geographical and socioecological scales.⁹³ As described in Aday and Andersen's access framework, access can be determined by assessing the influence of health policy, characteristics of the health delivery system, and characteristics of the population at risk, all of which occur at varying socio ecological levels.⁵⁸

Further examination of the access framework demonstrates that these factors could also lie on various geographical levels. For example, in most cases health policy varies by state and thus occurs at the state level, and characteristics of the health delivery system commonly vary by hospital/clinic and thus occur at a lower level such as county or region. Considering the hierarchical structure of the data allows researchers to simultaneously examine the effects of individual and group level variables and the interactions within and between them.⁹⁴ Further, this approach allows researchers to more accurately model reality by accounting for non-independence of individuals within groups.⁹⁴⁻⁹⁵ Finally, using this approach when appropriate

allows researchers to adjust for spatial heterogeneity or clustering thereby ensuring that standard errors and p-values for the estimated regression parameters are unbiased and the correct inferences are made. Ultimately, exploring the relationship between place-based contextual and compositional factors and health outcomes using multilevel models has proven to be extremely useful in understanding complex health issues.

Despite the efficiency of multilevel modeling, a review of the literature indicates that most of the studies on this topic limit their investigations to one level of influence at a time^{90-92, 96} and with the exception of the impact of the ACA, typically understudy the effects of several factors that lie at the health policy level. In fact, no study was found using multilevel modeling to understand multilevel access barriers and their effects on late stage CVC diagnosis. However, multilevel modeling has been used to assess other cervical cancer-related outcomes including: CVC screening, CVC incidence, CVC mortality, HPV coverage, and immune response to HPV vaccines. Among these studies, insurance status and percent living in poverty were the most commonly used access to care indicators. In fact, a 2005 study conducted by Datta et al. used multilevel modeling to examine individual, neighborhood, and state level predictors of cervical cancer screening among African American women in the US.⁹⁷ This study evaluated the effects of several covariates, however, insurance status and percent living in poverty were the only access indicators included in the model.⁹⁷ A more recent 2103 study also used a multilevel random intercept model to assess the impact of individual, county and region-level variables on HPV vaccination coverage among women in Texas.⁹⁸ This study also tested the effects of percent of uninsured and percent of total population in poverty.⁹⁸ A 2013 dissertation study also used multilevel modeling to investigate the effects of individual, area and county level factors on cervical cancer incidence among women in Appalachia Ohio.⁹⁹ Similar to previously mentioned studies, percent without health insurance and childhood poverty were the only access to care indicators included in this model.⁹⁹ Although none of these studies obviates the need for our research, Coughlin et al.'s study most closely aligns with our research study as they use the multilevel approach to examine the effects of individual and county level factors associated with health care access on breast and cervical cancer screening among women in the US.¹⁰⁰ These factors included health insurance coverage, residence in health professional shortage areas, and the number of health centers/clinics and primary care physicians.¹⁰⁰

Spatial Analytic Methods & Perspective

Finally, the literature suggests that advanced spatial analytic methods and perspectives have not been frequently applied to identify or generate hypotheses regarding the factors underlying racial and geographical disparities in stage at cervical cancer diagnosis. This is due in part to lack of knowledge regarding the utility of spatial data, lack of appropriate spatial databases and previously insufficient spatial analytic software.¹⁰¹ As a result, previous research on this topic largely underestimates the contribution of place; a “social context deeply connected to larger patterns of social advantage and disadvantage.”¹⁰²

Considering the contribution of place is essential to understanding health outcomes. Using spatial methods, researchers have assessed the distribution of disease incidence, mortality and stage at diagnosis rates across geographic regions to identify disparities and generate hypotheses regarding significant factors underscoring various health outcomes. In fact, a spatial method called Local Indicators of Spatial Association (LISA) testing allows researchers to evaluate area differences in rates of health outcomes by pinpointing spatial clustering of these rates at the county level. Specifically, counties are grouped into four distinct spatial cluster types: high-high, low-low, low-high or high-low clusters. If both a county and the spatial lag of that county (i.e. the average rate of all the defined neighbors of a county) are lower than the national average rate and there is a statistically significant correlation between them, it is classified as being within a low-low cluster (i.e. coolspot). Similarly, if both a county and the spatial lag of that county are higher than the national average rate and there is a statistically significant correlation between them, it is classified as being within a high-high cluster (i.e. hotspot). By focusing on clustering of counties with higher than average rates of a selected health outcome that are surrounded by neighboring counties with higher than average rates of that same outcome “hotspots,” researchers can determine 1) whether there are geographic disparities in the selected health outcome, 2) whether these geographic disparities persist over time and 3) whether they are associated with various contextual and compositional factors.

Based on a thorough review of the literature, this approach has never been applied to understanding disparities in late stage cervical cancer diagnosis and their associated risk factors. However, a similar approach has been applied to the investigation of disparities in cervical cancer incidence. Roche et al. used New Jersey state cancer registry data and applied spatial scan

statistics to identify spatial clusters of census tracts with high cervical cancer incidence.¹⁰³ After identifying these geographical disparities they used logistic regression to examine risk factors associated with being a census tract in a high rate cluster.¹⁰³ Similarly, a study conducted by Saghari et al. used geographic information systems (GIS) to evaluate spatial clustering of both cervical cancer incidence and SES in California.¹⁰⁴ To determine whether there was an association between patterns, the authors then tested spatial cross correlations between the identified cervical cancers incidence and SES clusters.¹⁰⁴ These examples demonstrate the usefulness of spatial methodology in understanding disparities in cervical cancer outcomes.

Summary of Limitations

The current literature evaluating disparities in late stage cervical cancer diagnosis is limited in a number of ways. Specifically, neither advanced spatial analytic methods nor multilevel modeling have been applied in studies aiming to identify factors underlying racial and geographical disparities in stage at cervical cancer diagnosis. Yet, both of these methods have been proven useful for public health surveillance and understanding disease etiology and disparities among an array of other health outcomes. Review of the existing literature on access to CVC screening and late stage CVC diagnosis also demonstrates that the impact of several constructs of the Access Framework has been left unexplored. However, using a thorough list of factors identified through the access to care framework is necessary for conceptualizing and gaining a comprehensive understanding of the impact of multilevel access barriers experienced along the pathway to late stage diagnosis. Finally, no study has used nearly complete US data (n=43 states) to explore these disparities and underlying factors. Most of the studies used single state registry data or SEER data, which only includes complete data from 12 states.

Statement of Purpose & Research Aims

The purpose of this study is to develop a comprehensive understanding of where and why disparities in late stage cervical cancer occur. Specifically, this study aims to determine whether racial and geographical disparities in late stage cervical cancer diagnosis exist (and persist) and how multilevel access barriers impact them. Further, this study aims to highlight the relationship between inadequate access to care and disparities in late stage cervical cancer diagnosis. Using access-related contextual and compositional factors as a focus, we plan to develop a better understanding of how to best intervene, who is in greatest need of intervention and how to better

inform health policy. Ultimately, these efforts will contribute to the long term goal of reducing disparities in late stage cervical cancer diagnosis and the resulting disparities in cervical cancer mortality.

This study will include cervical cancer cases diagnosed from 2005-2014 from the United States Cancer Statistics (USCS) database, available at the National Center for Health Statistics Research Data Center.¹⁰⁵ The USCS database is a population-based surveillance system of cancer registries with data representing 98% of the US population.¹⁰⁵ This database has information on demographics (age, gender, race, and ethnicity), tumor characteristics, and geographic location (county of residence) at time of diagnosis.¹⁰⁵ The confidentiality of data with geographic identifiers for county of residence is preserved by restricting access to researchers with approved research plans with analyses conducted inside secure federal Research Data Centers (RDCs). There is no access to the Internet from inside the RDC, and all results must be reviewed before they can be released from the RDC and published.¹⁰⁵

All states participate in the USCS registry system, however, five states do not allow use of county of residence information (Kansas, Minnesota, Illinois, Michigan and Missouri).¹⁰⁵ Therefore, we will exclude these five states and two additional states, Alaska and Hawaii, because of missing contextual data. Our final analysis will include 43 states and each of their counties. The study sample will be further restricted to exclude cervical cancer records when these cases were not their primary cancers or when records featured unknown cancer stage or unstaged cancer. This restriction resulted in 120,325 cervical cancer cases between 2005- 2014. Using this data we plan to carry out the following specific aims:

Specific Aim 1 - Using data representing 43 of the 50 states, we will identify and characterize clusters of counties considered to be high risk “hotspots” and clusters of counties considered to be low risk “coolspots”, during two 5 year time periods (pre- and post-2010). Under this aim, we will also determine whether the hotspots identified in both time periods are associated with various contextual and compositional factors and whether there were hotspots that persisted over both time periods. To identify spatial clustering of county level late stage cervical cancer diagnosis rates during two time periods we will use a spatial cluster method called Empirical Bayes (EB) adjusted LISA. This method first corrects for variance instability among late stage CVC rates and then computes local spatial autocorrelation

statistics. Specifically, the EB- adjusted LISA test will calculate a test statistic for each county indicating whether the late stage cervical cancer incidence rate in that county is statistically significantly higher or lower than the national average. If both a county and the spatial lag of that county (i.e. the average rate of all the defined neighbors of a county) are statistically significantly higher than the national average rate, it is classified as being within a hotspot cluster. Similarly, if both a county and the spatial lag of that county are statistically significantly lower than the national average rate, it is classified as being within a coolspot cluster.

To determine whether the identified clusters are associated with various contextual and compositional factors we will employ a series of t-tests. Specifically, for both periods, all hotspot clusters will be grouped together and all coolspot clusters will be grouped together and treated as two independent groups. We will then test for statistically significant differences in underlying compositional and contextual factors between the two groups (hot and coolspots clusters).

Finally, to determine whether there were geographic hotspots that persisted over both time periods (worse places) we developed a colocation map. To develop the colocation map we grouped counties into three categories: those that belonged to significant hotspot clusters in both periods (persistently hotspots), those that did not belong to significant hotspot clusters in either period (persistently non-hotspots), and those that transitioned into or out of a hotspot clusters (transitional hotspots). The coincidence of these three categories across the two time periods were then mapped using QGIS software (formerly known as Quantum GIS).

It is our hypothesis that there will be spatial clusters of higher than expected late stage cervical cancer diagnosis rates and that these clusters will differ across the two time periods. We also predict these clusters will contain geographic factors that can help better explain why late stage CVC varies across counties in the US and how risks change over time. Thus, identifying spatial patterns will ultimately allow us to better isolate risk factors and generate realistic and testable hypotheses regarding the relationship between “hotspots” and contextual/compositional factors that may underscore significant inequities in stage at CVC diagnosis and access to CVC screening services. Finally, identifying patterns in late stage cervical cancer will allow researchers to target areas in greatest need of intervention and better allocate intervention resources.

Specific Aim 2- Using data representing 43 of the 50 states from the interval 2010-2014, we will examine the relationship between late stage cervical cancer diagnosis and various individual- and county - level access predictors, with a primary focus on primary care physician (PCP) shortage and the number of community health centers (CHCs) and other publicly funded clinics. Considering that minority communities are disproportionately represented among medically underserved populations and that publicly funded clinics predominately serve minority populations, we also aim to determine whether the relationships between the number of Planned Parenthood clinics per 100,000 people and CVC stage at diagnosis and PCP shortages and stage at CVC diagnosis differ by race or ethnicity. With patients nested within counties, we expect that stage at cervical cancer diagnosis will be clustered within the spatial contexts of county. Thus, we will fit a two-level random-intercept logit model to examine various individual- and county-level predictors of late stage cervical cancer diagnosis.

Individual level predictors will include age and race or ethnicity. County level predictors will include number of CHCs and other publically funded health clinics per 100,000 people (Planned Parenthood (PPH) clinics and Federally Qualified Health Centers (FQHCs)), primary care physician shortage , percent uninsured, percent poverty, percent HMO penetration, previous country of residence and population density as a measure of urbanicity. We will also estimate two separate multilevel models each with the aforementioned covariates and a single cross-level interaction. One model will include a cross-level interaction between race or ethnicity and PCP shortage and the other will include a cross-level interaction between race or ethnicity and PPH clinics. Final random and fixed parameter estimates will be calculated using Maximum Likelihood estimation methods in SAS 9.2 statistical software. This model will provide national level estimates of the probability of late stage CVC given various access indicators.

Specific Aim 3- Using data representing 43of the50 states, we will identify **county-level disparities in late stage CVC across (n=43 states) and explain the observed disparities by identifying statistically significant ecological relationships between high proportions of late stage CVC diagnoses in counties and several county and state-level variables during the time interval 2010-2014. Using a hybrid model that draws from the Access to Care Framework, Theory of Access and Socio-ecological model, we specifically explore the**

relationships between late stage CVC and several indicators of access to CVC screening. Among the study variables we are most interested in are unexplored access to care factors that are determined by state policy including: state policies regarding scope of practice for nurse practitioners, state healthcare insurance CVC screening mandates and state-level proportions of individuals enrolled in self-insured employer-sponsored insurance plans.

With counties nested within states, we believe that stage at cervical cancer diagnosis will be clustered within the spatial contexts of state. Thus, we will fit a two-level random-intercept logit ecological model to examine various county and state level predictors of late stage cervical cancer diagnosis.

County level predictors will include the following contextual variables: number of PPH clinics, FQHCs, and Title X funded centers, Health Professional Shortage Area (HPSA) score, percent persistently poor, percent that speak English poorly and population density as a measure of urbanicity. County level predictors will include the following compositional variables: age and race or ethnicity. State level predictors will include Nurse Practitioner (NP) regulations, CVC screening mandate, percent of state underserved by primary care providers, percent screened for CVC and proportion insured by employers in self-insured plans exempt from state regulation. To identify interactive relationships associated with geographic disparities in late stage CVC diagnosis, we will also include a cross-level interaction between CVC screening mandates and percent in self-insured plans. Because private self-insured plans can avoid the protective effect of state health insurance mandates, we hypothesize that states with both CVC screening mandates and higher proportions of the state population in private self-insured plans will be associated with high county-level proportions of late stage CVC. Final random and fixed parameter estimates will be calculated using Maximum Likelihood estimation methods in SAS 9.2 statistical software, which will allow for state intercepts to vary.

To visualize geographic disparities in the proportion of late stage cervical cancer across counties, we will also spatially translate proportions onto a US map. Mapping will be done in QGIS software using standard deviation features which groups proportions by how many standard deviations (<2 sd : >2 sd) they are from the national estimate. It is our hypothesis that these place-based contextual and compositional factors are access to care barriers associated with higher proportions of late stage CVC diagnosis. We also believe that there are significant

geographic disparities in late stage CVC diagnosis and that these access barriers may help to explain why late stage diagnoses rates varies across counties.

Significance

Cancer stages represent the extent and spread of the disease. Cervical cancer stage at diagnosis is important as it plays a significant role in cervical cancer treatment, prognosis and survival.¹ Specifically, late stage (regional and distant) CVC is associated with increased morbidity and lower 5-year survival rates.¹ In fact, the 5-year survival rate for distant cervical cancer is as low as 17%, compared to a 5 year survival of 56% for regional cervical cancer and 91.7% for localized cervical cancer.¹⁰⁶

With 51% of cervical cancer cases diagnosed at a late stage³ it is important to understand the factors associated with late stage cervical cancer diagnosis and disparities. Without doing such CVC mortality rates will remain high and at a disproportionately higher rate for women in various geographical areas and African American and Hispanic women. Currently, cervical cancer mortality rates have been consistently higher among Blacks compared to all other race or ethnicity groups since 1999.¹⁰⁷ According to these national statistics, the overall cervical cancer (CVC) mortality rate among African American (AA) women in 2014 was 3.6 per 100,000 compared to 2.2 per 100,000 among the referent White women.¹⁰⁷ However, results of a recent study published in January 2017 suggests that after adjusting for hysterectomies the racial gap was found to be even wider than previously estimated, with overall CVC mortality rates increasing to 10.1per 100,000 among AA women compared to 4.7 per 100,000 among White women.¹⁰⁸ In regard to Hispanic women, the mortality rate is 2.6 per 100,000 women, compared to 2.0 per 100,000 among White women .¹⁰⁹ Similarly, a number of geographic areas are more heavily burdened with CVC mortality compared to other areas, with Alabama , Mississippi, Arkansas, West Virginia, Tennessee and South Carolina reporting disproportionately higher rates of CVC mortality at one of the highest geographical levels (i.e. state) .¹¹⁰ Eliminating such disparities are among this nation’s top priorities,³⁶ as reflected in Healthy People 2020’s (HP2020) goal “to achieve health equity, eliminate disparities, and improve the health of all groups.”¹¹¹

The proposed study will help support this goal by assessing the spatial distribution of late stage CVC diagnosis. The current literature lacks recent surveillance of late stage CVC in the complete US and no study has sought to identify concentrated areas of higher than average rates of late stage CVC “hotspots” across the US. These hotspots represent geographical disparities and can be used to target areas in need of intervention and generate hypotheses regarding significant risk factors. Also, by assessing whether geographic hotspots persist over time, we have the potential to target worse places and yield greater returns on prevention investments.

The proposed study will also make significant progress toward HP2020 goal of eliminating disparities by investigating the unknown relationships between disparities in stage CVC diagnosis and several understudied access to care constructs. To date no study has examined the relationships state NP regulations, state cervical cancer screening mandates, PCP shortage areas, rates of exempt self-insured employers, or publicly funded health center density have with late stage cervical cancer diagnoses. Similarly, no study has assessed whether these access indicators are risk factors underscoring significant racial and geographical disparities in stage at CVC diagnosis. However, given the substantial variation in the distribution of each of these variables across counties and states, and their known associations with CVC screening rates, each likely plays an important role in these disparities. Further, given the increased prevalence of ‘self-insured’ plans in states, which exclude large portions of the insured population from CVC screening coverage mandates, we believe self-insured plans may also play an important role in stage at diagnosis.⁵⁶

The results of this study can serve as reliable evidence supporting the need or furtherance of policies aiming to reduce the number of late stage CVC diagnoses. Additionally, by assessing both independent and interactive associations with stage at CVC diagnosis, we can also determine whether the benefits of health policies are greater among more vulnerable population groups. Ultimately, the long-term impact will be to inform policies to reduce disparities in late stage CVC diagnoses and mortality rates among minority women and women in specific geographic regions of the US.

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Chapter Two: Examining Spatial Clusters of High & Low Proportions of Late Stage Cervical Cancer in the U.S.: A Look at Geographic Disparities & Associated Risk Factors

Introduction

Prior to the introduction of Pap testing in the early 1950s, cervical cancer (CVC) was the most common cancer among women in the United States.¹ The ability to detect and treat precancerous cervical cell changes and early stage cancers through Pap test screening has made cervical cancer one of the most preventable of all cancers.² In fact, due to screening the incidence of cervical cancer decreased by more than 50% during 1975- 2014.³⁻⁴ Since the end of a sharp decline in 2001, however, CVC incidence rates have remained stable.⁴

Despite known effectiveness of Pap screening for early detection, recently available data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that 51% of women with cervical cancer were diagnosed at a late stage (regional or distant).⁵ Stage at diagnosis is a significant public health concern as it has been found to play a leading role in cervical cancer treatment, prognosis and survival.⁶ Specifically, late stage cervical cancer is associated with increased morbidity and lower 5-year survival rates.⁶ The 5-year survival rates for distant and regional cervical cancer are as low as 17% and 56%, respectively, compared to a 5 year survival of 91.7% for localized cervical cancer.⁷

Previous epidemiological surveillance using 2001-2003 county-level data from SEER and the North American Association of Central Cancer registries indicated that the percent of late stage cervical cancer was highest in Iowa, Connecticut, California, New Jersey and Missouri.⁸ A later report using 2004-2006 data from cancer registries affiliated with CDC's National Program of Cancer Registries (NPCR) and SEER indicated that late stage CVC incidence rates were highest in Arkansas, the District of Columbia, Illinois, Kentucky, Louisiana, Mississippi, Nevada, New Mexico, and Oklahoma.⁹ These studies suggest that the incidence and thus the burden of late stage CVC varies widely between states in the US. However, little is known about how the incidence and burden of late stage CVC differs within specific counties across each of the different states. A few studies have examined the county-level distribution of late-stage CVC incidence within a single state,¹⁰⁻¹³ however there is a lack of literature describing the distribution of late stage CVC at the county-level across the entire or majority of the US.

There are no current studies specifically assessing the spatial clustering of county-level late stage CVC rates across the entire US. Identification of county-level clusters of higher than average rates of late stage CVC “hotspots” would provide important new information to inform our approaches to reducing the burden of late stage CVC. Examining county as opposed to state-level data will help us to identify highly burdened places that are potentially masked when using aggregated state-level data. In addition, examining spatial clusters as opposed to simple geographic distributions of late stage CVC rates will allow us to generate and test hypotheses regarding underlying risk factors that may be common to counties within adjacent states.

Hotspot analysis is an essential technique used within geographic information system (GIS) studies. However, sophisticated spatial analytic methods such as these have not been frequently applied to identify late stage CVC hotspots or generate hypotheses regarding the factors underlying late stage diagnoses. This is due in part to a lack of knowledge regarding the utility of spatial data, lack of appropriate spatial databases, and previously insufficient spatial analytic software.¹⁴ As a result, previous research on this topic largely underestimates the contribution of place; a “social context deeply connected to larger patterns of social advantage and disadvantage.”¹⁵ To our knowledge, this is the first time this approach has been used to understand late stage CVC.

Using spatial cluster methods, our first aim is to examine geographic disparities in late stage CVC diagnosis rates in the US by robustly identifying and characterizing clusters of counties considered to be high risk “hotspots” and clusters of counties considered to be low risk “coolspots,” during two different time periods, both before and after implementation of the preventive services provisions of the Patient Protection and Affordable Care Act (ACA). Our secondary aim is to determine whether the hotspots identified in both time periods are associated with various contextual and compositional factors. Finally, our third aim is to determine whether there are geographic hotspots that persist over both time periods, as these places may represent those counties in more urgent need of intervention. It is our hypothesis that there will be spatial clusters of higher than expected late stage CVC diagnosis rates in the US and that clusters will differ across the two time periods. We also believe these clusters will contain geographic factors that can help better explain why late stage CVC varies across counties in the US and how risk changes over time.

Ultimately, identifying patterns in late stage CVC will allow us to pinpoint the areas in greatest need of intervention, to better allocate intervention resources and evaluate performance of existing prevention and early detection programs. These findings can also be used to inform further research aimed at gaining a better understanding of the underlying causes of late stage CVC. Finally, comparing spatial patterns and risk factors pre- and post-ACA implementation will allow researchers to generate hypotheses regarding the policy's impact and effectiveness as it relates to cancer prevention and control.

Methods

Study Population

This study includes cervical cancer cases diagnosed during the ten-year period from 2005-2014 from the United States Cancer Statistics (USCS) database, available at the National Center for Health Statistics Research Data Center. The USCS database is a population-based surveillance system of cancer registries with data representing 98% of the US population.¹⁶ This database has information on demographics (age, gender, race, and ethnicity), tumor characteristics, and geographic location (county of residence) at time of diagnosis.¹⁶ The confidentiality of data with geographic identifiers for county of residence is preserved by restricting access to researchers with approved research plans with analyses conducted inside secure federal Research Data Centers (RDCs).¹⁶ There is no access to the Internet from inside the RDC, and all results must be reviewed before they can be released from the RDC and published.¹⁶

All states participate in the USCS registry system, however, five did not allow us to use county of residence information (Kansas, Minnesota, Illinois, Michigan, and Missouri).¹⁶ Therefore, we excluded these five states and two additional states, Alaska and Hawaii, because of missing contextual data. Our final analysis includes 43 states and their 2,357 constituent counties. The study sample was further restricted to include all persons having cervical cancer and excluded records: when cases were not their primary cancers, when records featured unknown cancer stage or unstaged cancer. This restriction resulted in 120,325 individuals living with cervical cancer in the US during 2005- 2014. Cases were then divided into two 5-year time periods: those diagnosed during 2005-2009 (preACA), and those diagnosed during 2010-2014 (post ACA). We further categorized cases into late stage (regional and distant) or early stage (localized, including

in situ) diagnosis. We then created a county-level late stage diagnosis rate variable for both time periods, which was used to address study aim 1. This variable aggregated the total number of late stage cases within each county by Federal Information Processing Standard (FIPS) code and divided this by the total number of CVC cases. Multiplying by 100 converted these proportions into percentages.

In addition to the USCS's geographic location, case identification and stage variables, we also extracted two additional variables for use in study aim 2, race or ethnicity and age. We created six race or ethnicity variables representing the proportion of the population that was White, Black, Hispanic, Asian Pacific, American Indian or other. We also created five age variables representing the percent of the population that was either less than 40, 40–49, 50–64, 65–74, or 75 years or older. Additional county-level contextual variables needed for aim 2 were extracted from a number of external data sources. Data describing the percentage of the county population living in poverty (2005 and 2010), the percentage of individuals under age 65 with no health insurance (2005 and 2010) and the percent of individuals unemployed (2005 and 2010) were obtained from the U.S. Census Bureau, SAHIE data.¹⁷ The proportion of the population age 18–64 that speaks English poorly (2007–2011) and the percent of population who came to the US from a different country in the prior year variables were extracted from the American Community Survey.¹⁸ Data describing county level population density (i.e. urbanicity) was extracted from the Economic Resource Services (ERS) agency.¹⁹ This measure was calculated by dividing the total population in 2010 divided by the total square miles of land area. Higher values of this measure indicate more urban places.

The percent of the state population insured by employers in private self-insured health plans in 2010 was obtained from the Agency for Healthcare Research and Quality (AHRQ).²⁰ Data describing the percent of HMO penetration in 2010 was extracted from Kaiser.²¹ Finally, the number of federally qualified health centers (FQHCs) was extracted from the Guttmacher Institute's State- and County-level Family Planning Clinic dataset. We recoded the FQHC count variable into a rate per capita by multiplying each of the counts by 100,000 and dividing the product by the total US population in 2005 and 2010.²²

Statistical Analysis

Using Moran's I statistics computed using GeoDa software, we **robustly identify clusters of counties considered to be high risk "hotspots" and clusters of counties considered to be low risk "coolspots" across the US during two time periods (pre- and post-ACA implementation), aim 1.** Moran's I statistics are computed based on an underlying assumption of constant variance among rates, which can be violated when denominator population sizes vary a lot. Therefore, we first assess whether this assumption holds or is violated by developing histograms of the distribution of county populations used as the denominators in constructing the rates during both time periods and comparing them to a normal curve. Histograms show skewness in the distribution of the late stage CVC rates during both time periods, suggesting potential for variance instability (Figure 1) due to the fact that the underlying populations at risk (all women with CVC) vary in size across counties. Such variance instability in the rates can lead to spurious inferences for global and local Moran's I.²³⁻²⁴ To correct for variance instability among late stage CVC rates, we use Empirical Bayes (EB) standardization techniques to compute global and local spatial autocorrelation statistics. This method is known for adjusting these statistics for small sample sizes, reducing the variability of estimates, removing erroneously suggested spatial outliers and thus computing robust and reliable clusters.²³⁻²⁴ To accomplish EB standardization GeoDA computes spatial autocorrelation for transformed standardized random variable.²³ To get this transformed standardized variable GeoDa turns the crude rate for each observation into new variable that has a mean of zero and unit variance and thus accounts for instability in variance.²³

Global spatial autocorrelation was determined by performing the EB-adjusted global Moran's I spatial clustering test, which produces a EB Moran's I coefficient test statistic. Given a statistically significant EB Moran's I coefficient, we reject the null hypothesis of spatial randomness and conclude that there is global clustering in the patterns of late stage CVC rates across counties. After confirming that there was global clustering we calculated EB-adjusted Local Indicators of Spatial Association (LISA) to pinpoint the specific locations of the statistically significant clusters within both time periods. At significance level <0.05 , the EB LISA test first calculates a test statistic *for each* county representing whether the county has a statistically significant higher or lower than the national average rate of late stage CVC.

To determine statistical significance of EB LISA test statistics, GeoDA uses a permutations approach called bootstrapping. This approach compares the actual correlation between late stage CVC measures among a county and its neighbors with 1000 or more correlations between the county in question and groups of randomly chosen neighbors. Queen contingency matrix weights are used to define neighboring counties. A statistical distribution is generated by the more than 1000 permuted repetitions with the random neighbors and is assessed to determine where along the distribution the actual correlation falls. If the actual correlation with neighbors falls in the tail of the distribution then we reject the null hypothesis of local spatial randomness and conclude that the county's correlation with actual neighbors is statistically significantly unlikely to have occurred by chance. This assessment is repeated independently for each county in the dataset, and the collection of test statistic findings for all counties are mapped together in a single LISA clustering map.

Using statistically significant EB LISA test statistics, four distinct cluster types are formed in both time periods: high-high, low-low, low-high and high-low. High-high clusters include counties with higher than average rates surrounded by other counties with higher than average rates. Similarly, low-low clusters include counties with lower than average rates surrounded by other counties with lower than average rates. Low-high and high-low clusters are developed in a similar fashion. Among all cluster types, those that were statistically significant were presented in two separate maps, one for each time period, using QGIS software. To represent the entire cluster both maps included the counties at the center of the cluster and their surrounding neighbors. **To determine whether the hotspot clusters identified during both time periods were associated with various contextual and compositional factors, aim 2**, we employed two sets of independent sample t-tests in SAS version 9.0. Specifically, for both time periods, we grouped all high-high clusters together and all low-low clusters together and treated them as two independent groups. We then tested for statistically significant differences in the means of the underlying biological and contextual factors between the two cluster groups.

Finally, **to determine whether there were geographic hotspots that persisted over both time periods, aim 3**, we developed a colocation map. To develop the colocation map we grouped counties into three categories: those that belonged to significant hotspot clusters in both periods (persistently hotspots), those that did not belong to significant hotspot clusters in either period

(persistently non-hotspots), and those that transitioned into or out of a hotspot clusters (transitional hotspots). The coincidence of these three categories across the two time periods was then mapped using QGIS software.

Results

LISA Cluster and Persistent Hotspot Results (Figures 1-3)

Empirical Bayes (EB) adjusted Global Moran's I tests indicate that there is significant positive spatial autocorrelation among the proportions of late stage CVC during both time periods, (significance level $\alpha=0.05$). Thus, for both time periods, we reject the null hypothesis of spatial randomness and conclude that the proportions of late stage CVC across neighboring counties were too similar in some local areas to have occurred by chance.

Using EB adjusted Local Moran's I tests, we further determined which local areas were statistically significantly spatially correlated with one another with regards to late stage CVC proportions- location of local clusters. During both time periods, we found several statistically significant local high and low rate cluster centers. High-rate clusters centers are areas where counties and their neighbors have statistically significantly higher proportions of late stage CVC than would be observed by chance, using a 5% level of significance. These clusters will be referred to as "hotspots" going forward. Low-rate clusters centers are areas where counties and their neighbors have statistically significantly lower proportions of late stage CVC than would be observed by chance, using a 5% level of significance. These clusters will be referred to as "coolspots" going forward.

During 2005-2009, we found 111 statistically significant hotspots (colored red) and 77 statistically significant coolspots (colored blue). Hotspots were observed in 24 of 43 states but were most apparent throughout the Eastern and Southern regions of the US, as well as California, Colorado, Connecticut, Massachusetts and Wyoming. Coolspots were observed in 23 of 43 states but were most apparent throughout the Eastern and Southern regions of the US, as well as Oregon, Florida, Georgia and Oklahoma. (Figure 1)

During 2010-2014, we found 89 statistically significant hotspots (colored red) and 93 statistically significant coolspots (colored blue). Hotspots were observed in 19 of 43 states but were most

apparent in Florida, Pennsylvania, Oklahoma, New York and other states within the Southern and Eastern regions of the US. Coolspots were observed in 26 of 43 states but were most apparent in Georgia, Arizona, Utah, Oregon, Washington and other states within the Eastern region of the US. (Figure 2)

Over time the number of statistically significant hotspot clusters decreased while the number of statistically significant coolspot clusters increased. However, colocation mapping shows that there were 56 hotspot clusters that persisted overtime. Persistent hotspot clusters were observed in 13 of 43 states and were most apparent in California, Louisiana, Alabama and Georgia. (Figure 3)

Comparison of High and Low Rate Clusters: T-test Results (Table 1-2)

To determine what factors were associated with hotspot clusters, we tested for significant differences in the means of the underlying compositional and contextual between the hotspot and coolspot clusters observed in both time periods. During the early period, we found that hotspot clusters had a statistically significantly higher proportion of women who were White, Asian and individuals less than age 50 among the CVC sample population, compared to coolspot clusters. Hotspot clusters in the early period also had a statistically significantly higher proportion of counties that were underserved by a primary care provider, compared to coolspot clusters. In addition, compared to coolspot clusters, hotspot clusters had statistically significantly lower proportions of African American women among the CVC sample population, and lower proportions of unemployed persons and 18-64 year olds that spoke English poorly in the general population. Finally, we found that hotspot clusters in the early period had a statistically significantly lower proportion of HMO penetration. (Table 1)

When comparing hotspot and coolspot clusters observed during the later period we found drastically different associations than what was found when comparing cluster groups observed during the early period. During the later period, we found that hotspot clusters had a statistically significantly higher proportion of people that were in poverty, unemployed, and in self-insured insurance plans that were exempt from state regulations. Compared to coolspot clusters, hotspot clusters also had a statistically significantly higher proportion of African American women in the CVC sample women and a higher proportion of counties that were underserved by a primary

care provider. We also found that hotspot clusters had a statistically significantly lower proportion of White and Asian women as well as individuals less than age 50 in the CVC sample population, compared to coolspot clusters. During the later period, the percent of HMO penetration was also statistically significantly lower in hotspot clusters compared to coolspot clusters. (Table 2)

Discussion

Although the number of CVC cases has decreased over time, the proportion of CVC cases diagnosed at a late stage has increased from 47% to 54% overall. This highlights the need to identify former, existing and persisting clusters of high proportions of late stage CVC and to determine what factors are associated with these clusters. The results of this study are essential for pinpointing areas in need of intervention and generating hypothesis regarding the causes of late stage CVC.

The LISA clustering method is a sophisticated spatial method used to identify areas in need of intervention by pinpointing areas of local clustering of rates. This method has been used to identify high risk areas in a number of studies²⁵⁻²⁶ However, this method assumes constant variance in the rates across the areas, which was not the case for our study measure. This was due to there being small counts in both the numerator (CVC cases diagnosed at a late stage) and denominator (all CVC cases) of the proportion of late stage CVC variable. To ensure that this did not bias the clustering results we employed a more robust LISA technique called Empirical Bayes (EB) adjusted LISA. This method has never been used to identify clusters of high proportions of late stage CVC. However, there were significant differences in the location of clusters when EB and traditional LISA methods were used, which emphasize the importance of adjusting for variance instability in order to properly identify clusters. For example, using traditional LISA methods there were hotspot clusters observed in Montana and North Dakota during the early period (Figure 4). However, using EB adjusted LISA methods there were no hotspot clusters observed in either Montana or North Dakota during the early period. (Figure 1) This suggests that the late stage CVC LISA results were overestimated when traditional LISA techniques were used. Therefore, we take clusters observed using EB adjusted LISA to be most reliable and robust.

Using EB adjusted LISA, we found that there were substantial changes in the number and distribution of clusters over time and that the distribution of hotspots were not consistent with the state-level burden of late stage CVC identified in previous literature. Maps of EB adjusted LISA clusters show that the overall number of hotspots decreased from 111 to 89 over time while the number of coolspots increased from 77 to 93 over time. Maps also show that hotspots observed in Massachusetts, Connecticut, Wyoming and Colorado during the early period were no longer observed in the later period. We also found that over time local areas in both Utah and Arizona developed coolspots. On the other hand, some places such as Florida, Oklahoma and Pennsylvania developed hotspots over time. There are also areas in California, Louisiana, Alabama and Georgia that presented hotspots during both time periods.

There are several implications that can be drawn from the changes in the distribution of clusters over time. Local clustering of proportions into significant hot and coolspots during both the early and late period suggests that there were and still are geographic disparities in the proportion of late stage CVC across counties and states. It can also be implied that places that developed coolspots or lost hotspots over time may have implemented effective CVC interventions or early detection programs that worked to attenuate the geographic disparities that were once present. On the other hand, it can be implied that places with newly developed hotspots likely represent those places where there was a release in the pent-up demand for CVC screening services overtime. During the early period (2005-2009), there was a pent-up demand for CVC screening across the US due to a number of women having limited or no health insurance coverage. However, during the later period (2010-2014), millions gained access to CVC screening services via Affordable Care Act (ACA) provisions that mandated full coverage for preventative services in 2010²⁷ and expanded Medicaid in 2014.²⁸ Thus, newly developed hotspots are likely driven by a higher number of women being screened for CVC and in turn a higher number of diagnoses overtime. Lastly, places displaying persist hotspots overtime such as those observed in California, Texas and Southeast regions of the US represent those places in greatest need of interventions.

Implications can also be drawn from the comparisons of the differences in the means of contextual and compositional variables between hotspots and coolspots. The early period t-test results indicate that the percent of sample women with CVC who were Asian and White and

women under the age of 50 was significantly higher in hotspot clusters compared to coolspot clusters. However, this association changed over time. During the later period, the percent of sample women with CVC who were African American and women over the age of 50 became significantly higher and the percent of sample women with CVC who were White or Asian became significantly lower in hotspot clusters compared to coolspot clusters. These findings are consistent with the current literature which suggests that African Americans, Hispanics and women over 50 are now among those disproportionately burdened by late stage CVC.²⁹⁻³⁰ Additional research is needed to understand why African American women and women over 50 are at greatest risk for late stage CVC. Similarly, additional research is also needed to understand what preventive programs, policies of behavior changes are associated with decreased risk of late stage CVC among Asian and White women over time. This information could be useful for developing intervention strategies among other race or ethnic populations.

In addition to the associated compositional factors, we also found that several factors that were not associated with hotspot clusters in the early period showed a significant relationship with hotspot clusters over time. Specifically, we found that the percent uninsured, unemployed, in poverty and insured by employers in self-insured plans exempt from state regulations became statistically significantly higher in hotspot clusters compared to coolspot clusters over time. These results suggest that overtime the proportion of late stage CVC became more strongly influenced by barriers to access to care, as a higher percent of unemployed, uninsured, those in poverty, individuals insured by employers in self-insured plans exempt from state regulations, and individuals underserved by a primary care provider, each represent access to care barriers.

Although coverage and cost sharing provisions were implemented under ACA between 2012-2014, we were not surprised to find that several access to care barriers were associated with higher proportions of late stage CVC during the 2010-2014 time period. The ACA has made significant strides toward improving access to CVC screening, however, it has not eliminated access barriers for all women. Following the implementation of the ACA, there were still 44.4 million individuals left uninsured and thus potentially facing issues regarding access and affordability of care.³¹ Furthermore, the shortage of primary care physicians (PCP) is projected to increase to as many as 49,300 PCPs by the year 2030.³² This presents a potential barrier to access to healthcare for women in the US, including those with insurance, as the US is already

experiencing a PCP shortage. Together these unresolved issues of affordability and availability of care can significantly shape access to CVC screening and thus stage at diagnosis. This demonstrates the need to further develop strategies to combat the issue of access to care, as the protective effects of the ACA are limited.

Together these results demonstrate that there are both geographic and demographic disparities in late stage CVC. Study results also suggest that late stage cervical cancer incidence and geographic disparities are likely influenced by county- and state-level factors, as clusters vary across counties and states. Results further demonstrate that the county-level factors associated with the current burden of late stage CVC are all indicators of access to care. These indicators include employment status, insurance coverage, poverty level, primary care shortage, HMO penetration and insurance plan exemptions from state-based health regulations. Advanced inferential statistics are needed to further investigate the relationships between various county- and state-level access to care barriers and late stage CVC incidence and disparities. More specifically, these relationships should be further investigated using mixed modeling methods which consider the hierarchical structure of the data. Using this approach the researcher can simultaneously examine the effects of county and state level variables and the interactions within and between them.

Without further investigation into these relationships the overall proportion of late stage CVC in the US will remain high and at a disproportionately higher rate among African American and Hispanic women and women in the identified hotspot clusters across the US. Stage at diagnosis is of significant public health concern as it plays a leading role in cervical cancer treatment, prognosis and survival.⁶ In fact, the 5-year survival rate for distant and regional cervical cancer is as low as 17% and 56% respectively, compared to a 5 year survival of 91.7% for localized cervical cancer.⁷ The results of the current study will help to reduce the number of late CVC cases and associated mortality by informing further research aiming to gain a better understanding of the underlying causes of late stage CVC. This study also pinpoints areas in greatest need of late stage CVC interventions, by identifying geographic hotspots that persist over both time periods, as seen in states including California, Louisiana, Alabama and Georgia.

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Figure 1

Results of Empirical Bayes LISA Cluster Analysis of the Proportion of Late Stage CVC Cases out of all CVC Cases in the U.S. during 2005-2009 (Early Period)

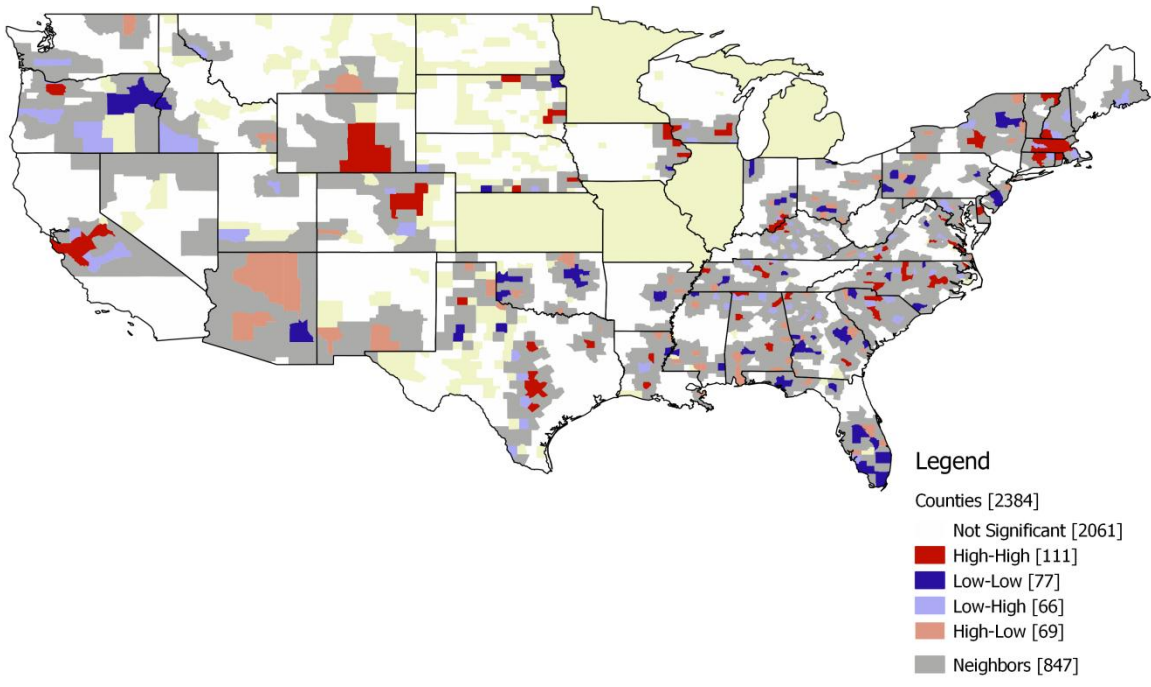


Figure 2

Results of Empirical Bayes LISA Cluster Analysis of the Proportion of Late Stage CVC Cases out of all CVC cases in the U.S. during 2010-2014 (Late Period)

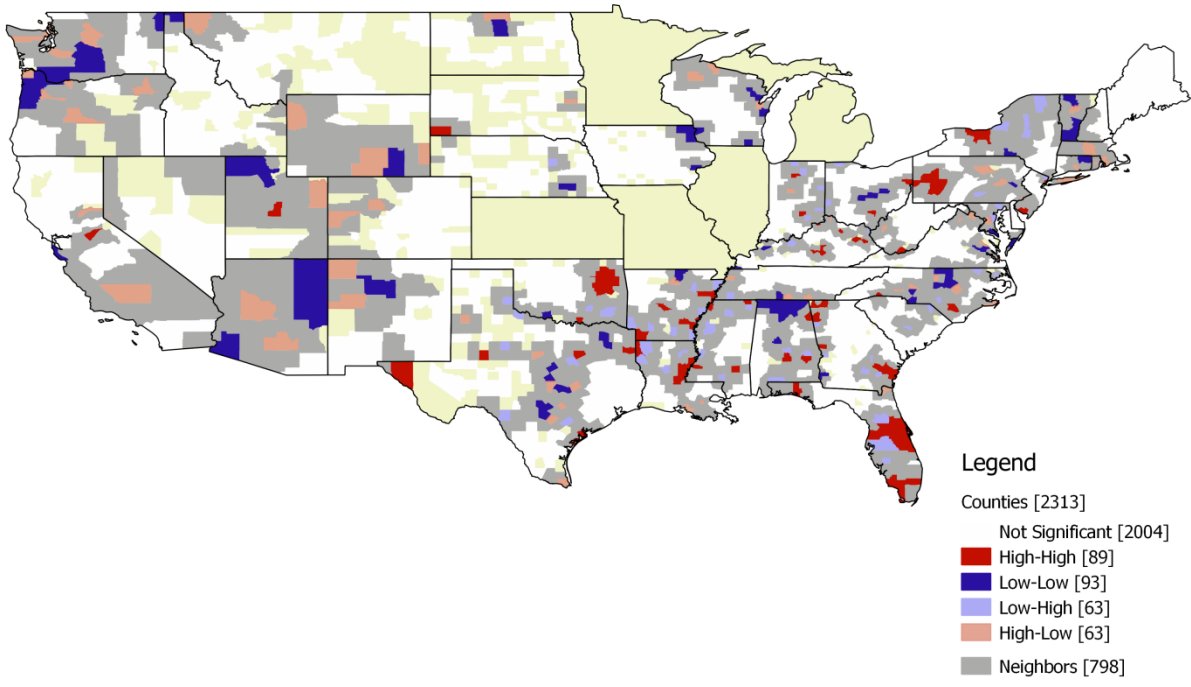
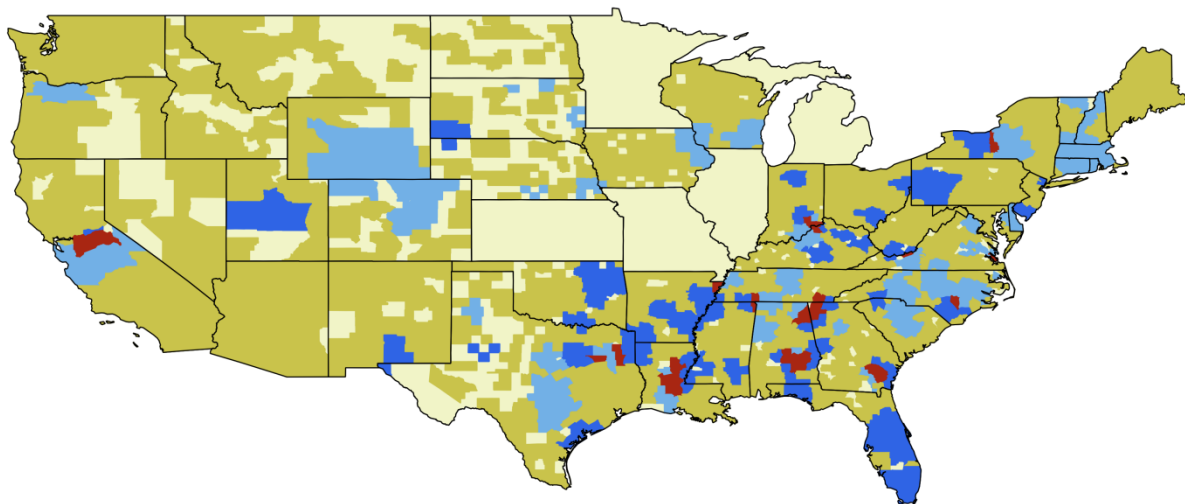


Figure 3

Empirical Bayes (EB) LISA Hotspot Clusters for Late Stage CVC Proportions that Coincide Geographically in Early Period (2004-2009), in Late Period (2010-2014), and in Both Periods

**Legend**

Counties [3097]

Not a Spatial Hotspot cluster [1547]

Hotspot Cluster in Early Period [320]

Hotspot Cluster in Late Period [293]

Hotspot Cluster in Both Periods [56]

Table 1 : T-test Comparing the Mean of Contextual and Demographic Variables Between EB adjusted Hotspot and Coolspot Clusters during 2005-2009

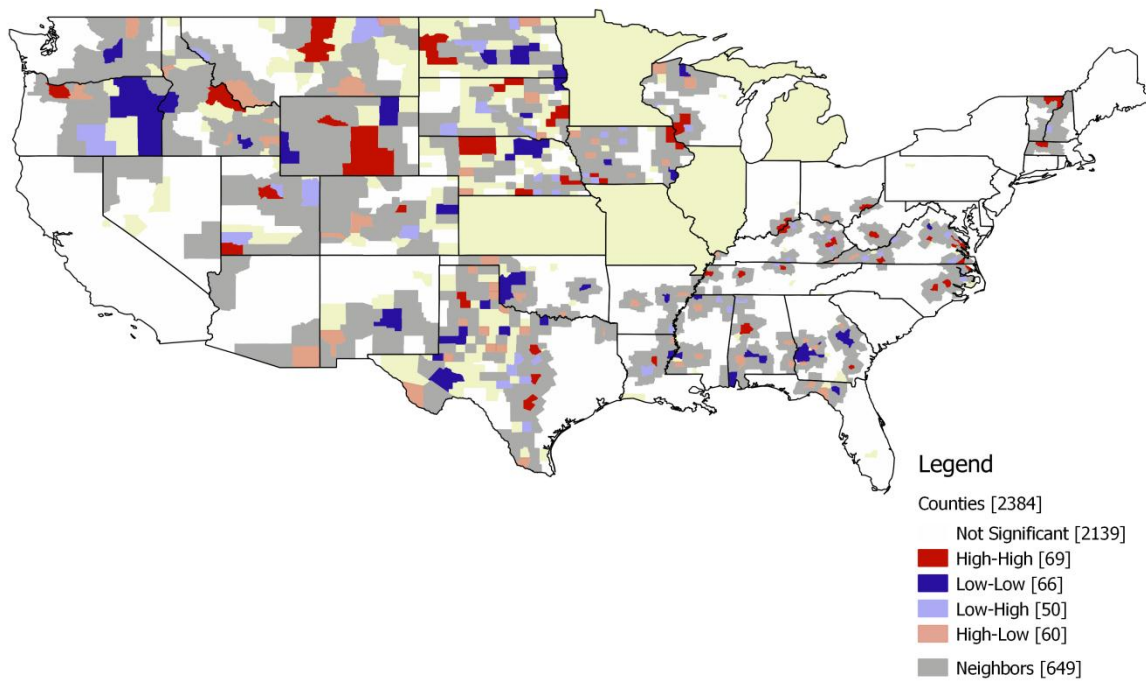
	Variable Description	Mean in Hotspots (N= 385)	Mean in Coolspots (N=339)	P value, for t-test of differences in means
Contextual Characteristics of Counties of Residence				
Under05	Percent underserved by a Primary Care Provider, 2005	46.9216	45.0018	<.0001
Xpoorne	Poor English Speaking among 18-64 year old (proportion)	0.1291	0.1448	0.0347
Xpov05	Percent of people of all Ages in Poverty for Income year 2005	3.58	3.36	0.5678
Xself06	Percent insured by Employers in Self-Insured Plans Exempt from State Regulations 2006	26.78	27.53	0.5979
Xune05	Percent Unemployed 2005	9.32	12.01	0.0075
Xhmo05	Percent HMO Penetration 2005	5.0935	5.7215	<.0001
Xuni05	Percent of total pop <65 uninsured 2005	9.38	10.72	0.1462
MovedCe	Percent of population that moved from different country last year	0.3209	0.2984	0.0030
Pop05/Land	Population Density 2005 (urbanicity)	349.4	228.5	0.1051
Sample Population Demographic Characteristics				
Agels50	Percent under age 50	55.93	50.14	0.0003
Aian	Percent American Indian	9.74	9.62	0.2675
Black	Percent Black	12.16	17.80	0.0005
Asian	Percent Asian	1.58	0.751	0.0025
White	Percent White	76.84	71.81	0.0082
Hispanic	Percent Hispanic	2.29	2.62	0.4992

Table 2 :T-test Comparing the Mean of Contextual and Demographic Variables Between EB adjusted Hotspot and Coolspot Clusters during 2010-2014

	Variable Description	Mean in Hotspots (N= 350)	Mean in Coolspots (N=335)	P value, for t-test of differences in means
Contextual Characteristics of Counties of Residence				
Under12	Percent underserved by a Primary Care Provider, 2012	13.0312	10.9681	<.0001
Xpoornl	Poor English Speaking among 18-64 year old (proportion)	0.0191	0.0216	0.5614
Xpov10	Percent of people of all Ages in Poverty for Income year 2010	18.61	14.50	<.0001
Xself13	Percent insured by Employers in Self-Insured Plans Exempt from State Regulations 2013	62.3106	60.5290	0.0003
Xune10	Percent Unemployed 2010	10.4811	9.2087	<.0001
Xhmo10	Percent HMO Penetration 2010	13.5544	16.5991	<.0001
Xuni10	Percent of total pop <65 uninsured 2010	20.1954	17.3681	<.0001
MovedCe	Percent of the population that moved from a different country	0.297	0.379	0.0098
Pop10/Land	Population Density 2010(urbanicity)	451.3	336.7	0.5989
Sample Population Demographic Characteristics				
Agels50	Percent under age 50	45.55	53.51	<.0001
Aian	Percent American Indian	1.77	2.67	0.2345
Black	Percent Black	16.78	8.38	<.0001
Asian	Percent Asian	1.12	1.91	0.0150
White	Percent White	72.59	76.76	0.0394
Hispanic	Percent Hispanic	7.04	9.45	0.0504

Figure 4

Results of Simple LISA Cluster Analysis of the Proportion of Late Stage CVC Cases out of all CVC Cases in the U.S. during 2005-2009 (Early Period)



Chapter Three: Availability and Affordability of Care Influencing Late Stage Cervical Cancer Diagnoses and Disparities in the U.S.

Introduction

Recent data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that 51% of women with cervical cancer (CVC) were diagnosed at a late stage (regional or distant),¹ an outcome associated with increased morbidity and mortality.² Epidemiological surveillance suggests that women who are over the age of 50,³ African American,³⁻⁴ Hispanic,³ and those residing in specific geographic regions of the US are more likely to have CVC diagnosed at a late stage.³ Foreign born women,⁵ women without health insurance,⁶ and women with lower incomes are also more likely to report late stage CVC diagnosis.⁷

Studies have shown that women who are screened for cervical cancer (CVC) are significantly less likely to be diagnosed at a late stage.⁸⁻¹⁰ In fact, recent studies suggest that the most significant predictor of stage at CVC diagnosis is current screening defined as having a Pap smear within the past three years.¹¹⁻¹³ Utilization of cervical cancer screening is largely attributed to access to care¹¹⁻¹³ and there are a number of identified barriers women face in obtaining this service,¹⁴⁻²² with some women experiencing greater challenges than others.²³ Studies suggest that women experience unequal access to CVC screening due to factors related to: insurance and employment status, income, distance to nearest primary care clinics, schedule availability, transportation costs and lack of a usual source of health care.¹⁴⁻²²

The implementation of the Patient Protection and Affordable Care Act (ACA) has helped to mitigate the issue of poor access to CVC screening by expanding access to health insurance to more than 20 million individuals in the US.²⁴ In addition, the ACA mandated that all health insurance plans were required to cover CVC screening in full, without cost-sharing (copayments or out of pocket costs) to insureds. As a result, the ACA has been shown to be associated with increased CVC screening rates and early stage diagnoses.²⁵⁻²⁶ A 2016 study reported that the ACA was associated with a 21.2% increase in early stage (stage I) cervical cancer diagnoses among cancer patients aged 19-25 years.²⁵ A systematic review of 14 studies in 2017 also found that the ACA had a significant impact on cancer screening, including Pap tests.²⁶

Although the ACA has made significant strides toward improving access to CVC screening, it has not eliminated access barriers for all women. Following the implementation of the ACA, there were still 44.4 million individuals left uninsured and thus potentially facing issues regarding access and affordability of care.²⁷ Furthermore, the shortage of primary care physicians (PCPs) is projected to increase as demand outpaces supply.²⁸ This presents a potential barrier to access for women, including those with insurance, as the US is already experiencing a PCP shortage.²⁹ Together these unresolved issues of affordability and availability of care can significantly shape access to CVC screening and thus stage at diagnosis. The current literature is in need of data describing how PCP shortage and factors associated with affordability of care for uninsured women are associated with stage at CVC diagnosis.

Availability – Primary Care Physician Shortage

Over time, data have consistently demonstrated the unmet need for additional primary care physicians in the US. According to the Association of American Medical Colleges (AAMC), there were an estimated 91.7 primary care physicians per 100,000 people in the US in 2016.³⁰ This translates to a total supply of approximately 296,353 primary care physicians.³⁰ Based on the current supply, there were 7,176 designated primary care health professional shortage areas (areas with ≤ 1 primary care physician per 3,500 people) in the US in 2017.³¹ Current Health Resources and Services Administration (HRSA) reports project that this shortage will be exacerbated as the population grows and as expanded insurance coverage provisions of the ACA take effect.²⁸ In fact, the PCP shortage is expected to increase to between 14,800 and 49,300 primary care physicians by year 2030.²⁸

The primary care physician shortage is of grave public health significance as leaving individuals without readily available care can impact a wide range of health outcomes. Research suggests that for every additional PCP per 10,000 there is a 5.3% decrease in all-cause mortality per year.³¹ Research also suggests that the physician shortage is a key determinant of disparities in access to care. With over 100 million Americans medically underserved,³² these individuals report a lower quality of health services and are less likely to receive routine medical procedures, including screening.³³ In fact, compared to women living in areas of higher physician density (500 or more office-based primary care physicians per 100,000), women who

live in areas of lower physician density (<100 office-based primary care physicians per 100,000 women) were significantly less likely to receive a Pap test in the past 3 years.³⁴⁻³⁵

Affordability- Community Health Centers & Publicly-Funded Clinics

Community health centers (CHC) were developed with the specific goal of providing high quality and comprehensive primary care to medically underserved populations, regardless of their ability to pay.³⁶⁻³⁷ Both CHC and other publicly-funded clinics provide free or low-cost services through a number of publicly funded programs including Title X family planning grants and the Medicaid program.³⁶ Grantee sites include federally qualified health centers (FQHC), Planned Parenthood affiliates, public health departments, hospitals and other health care providers. These sites provide a wide range of primary and preventive services, including cervical cancer screening, to individuals who are disproportionately uninsured, low income, and racial or ethnic minorities.³⁸

Community health centers and other publicly funded clinics are not evenly distributed across the US.³⁹ For example, some states have as many as 176 community health centers while others have a few as four.³⁶ The number of active community health centers is essential to public health as they play a critical role in providing access to care and reducing health disparities among their patient population of nearly 27 million.³⁶ Research further indicates that Title X-funded centers alone (including both CHC and publicly-funded clinics) were responsible for providing affordable CVC screening to more than 743,000 female clients across 3,900 Title X-funded health clinics in 2015.⁴⁰ Data also suggest that community health centers, irrespective of funding source, have been successful in expanding access to CVC screening and reducing related health disparities among their socioeconomically and racially diverse patient populations. In fact, health centers have provided 4% more Pap smear services to women in need of these services over the last 3 years compared to other health facilities.³⁶ Data also suggest that 92% of Hispanic women in need of a Pap test at health centers actually received these services compared to only 69% of Hispanic women in need of these services nationally who actually received them.³⁶ Similarly, 89% of African American women in need of a Pap test at health centers actually received these services compared to only 75% of African American women in need of these services nationally who actually received them.³⁶ Thus, these centers and clinics appear to serve a disproportionate share of the minority women in need.

The purpose of this paper is to determine whether late stage diagnosis of CVC is associated with PCP shortage and the number of CHCs and other publicly funded clinics that provide services at low or no cost per 100,000 people. Considering that minority communities are disproportionately represented among medically underserved populations and that publicly funded clinics predominately serve minority populations, we also aim to determine whether the relationships between the number of Planned Parenthood clinics per 100,000 people and CVC stage at diagnosis and PCP shortages and stage at CVC diagnosis differ by race or ethnicity. It is our hypothesis that these multilevel factors act as access to care barriers associated with higher odds of late stage CVC diagnosis. We also believe that there are significant racial disparities in late stage CVC diagnosis and that these access barriers may help to explain them. Although assessing the influence of the interaction between race or ethnicity and FQHCs would have also provided useful information, data describing the influence of FQHCs on racial disparities in CVC outcomes already exists. However, to our knowledge there are no studies that have assessed the relationship between racial disparities in stage at CVC diagnosis and Planned Parenthood clinics. Thus, we contribute to the current literature by investigating this unexplored relationship along with others. This study can provide evidence informing health policies aiming to reduce racial disparities in stage at CVC diagnosis by addressing the number of PCPs and publicly funded clinics in minority communities across the US.

Methods

Conceptual Model

The literature indicates that many health outcomes such as access to screening and subsequent disparities in stage at diagnosis are influenced by complex and interacting social, environmental and behavioral processes that occur at varying geographical and socioecological scales.⁴¹ Several researchers have reported that despite efforts to change, many health disparity studies have continued to focus solely on individual level explanations and have failed to include explanations of the spatial processes and pathways to health outcomes.⁴²⁻⁴⁴ However, failing to account for multilevel factors and spatial processes, when they present, has been found to significantly bias regression estimates.⁴⁵

To address the concerns raised in the recent literature and achieve unbiased estimates, we developed a multilevel conceptual model for understanding access to CVC screening and late stage CVC outcomes by drawing from the current literature and both Aday and Andersen's 1974 Access Framework⁴⁶ and Penchansky and Thomas's 1981 Theory of Access.⁴⁷ This hybrid model describes the influence and cross-level interactions among two levels. Level 1 includes individual factors that vary from person to person. The individual factors included in the model were mostly selected to represent what Aday and Andersen define as predisposing and enabling/disabling characteristics of the population at risk. Unfortunately, enabling/disabling characteristics such as information regarding personal income or insurance status is not available for the CVC cancer population. Thus, we only include the predisposing characteristics age and race or ethnicity. Level 2 includes healthcare market factors which vary across counties. The health market factors included were selected to reflect what Penchansky and Thomas define as availability, affordability and accessibility factors. Factors representing the affordability of care include CHC and publicly funded clinics, persistent poverty and percent uninsured. Factors representing the availability of care include PCP shortages and English language proficiency. Finally, accessibility is represented by the population density variable which is a measure of urbanicity. Each of the variables in the model have been found or are hypothesized to influence stage at CVC diagnosis. However, more aspects are listed than can be modeled using currently available data or computing power. We describe the specific variables used and a rationale for using them below.

Table 1: Descriptive of Study Variables

Variables	Description of Measures & Source	Rationale
Dependent Person-Level Variable		
Late Stage CVC Diagnosis	CVC cases diagnosed during 2010-2014 were categorized into late stage (regional and distant) or early stage (localized, including in situ diagnosis. Created dichotomous variable for late stage diagnosis Y/N. (USCS) ⁴⁸	Early detection and treatment of cervical cancer can significantly reduce the probability of cancer mortality. ² However, stage at diagnosis is associated with a number of factors, with barriers related to utilization of timely cancer screening being among top predictors. ¹¹⁻¹³
Independent Person-Level Variables (Level 1)		

Race or Ethnicity	Race or ethnicity categorized into 6 groups (non-Hispanic White, non-Hispanic Black, Hispanic, Asian and American Indian, and other) with non-Hispanic White as the reference group. (USCS) ⁴⁸	African American and Hispanic women have the highest incidence of CVC, are significantly less likely to be screened for CVC and are more likely to be diagnosed at a late stage, compared to all other races. ^{3-4,49}
Age	Age categorized into two groups: less than 50 (reference) and 50 and older. (USCS) ⁴⁸	Women over the age of 50 are significantly more likely to be diagnosed at a late stage. ³

Independent County-Level Variables (Level 2)

Percent Uninsured	Percentage of individuals under age 65 with no health insurance in 2010. (U.S. Census Bureau, SAHIE data) ⁵⁰	Health insurance status and type are significant predictor of both late stage CVC and access to CVC screening. ⁶ We control for health insurance coverage for women up until age 65, the cut off age for recommended CVC screening. ⁵¹
Moved From Different Country	Percent of population who came to the U.S. from a different country last year 2007-2011. (ACS) ⁵²	Recent immigration status is a significant barriers to CVC screening among Hispanic populations. ⁵³⁻⁵⁴
Urbanicity	Population density in 2010 (ERS) ⁵⁵	Women in rural areas and those in economically deprived non-rural communities are less likely to screen for CVC and report lower screening rates compared to women in urban and suburban areas. ^{17,53}
Percent Poverty	County level variable of percent of individuals of all ages in poverty in 2010. (ACS) ⁵²	Women with lower income and are more likely to be diagnosed at a late stage. ⁷
HMO Penetration	County-level variable of percent HMO penetration. (Kaiser)	Health insurance status and type are significant predictor of both late stage CVC and access to CVC screening. ⁶
Federally Qualified Health Centers	The county number of FQHCs per 100,000 people in 2013. (Guttmacher Institute) ^{56*}	The primary interest of this paper is the influence of CHC, publicly funded health centers and PCP shortage on both stage at CVC diagnosis and racial disparities in CVC diagnosis, which has never been explored. As described above, we believe the heterogeneity in these variables across counties plays a huge role in access to CVC screening and pathway to late stage CVC diagnosis and disparities.
Planned Parenthood Clinics	The county number of Planned Parenthoods per 100,000 people in 2013. (Guttmacher Institute) ^{56*}	
	*Multiplied each of the counts by 100,000 and divided the product by the total U.S. population for each county in 2010 to get count	

PCP Shortage	<p>per 100,000 people.</p> <p>Number of full-time equivalent (FTE) PCPs needed in the Health Professional Shortage Area (HPSA) so that it will achieve the population to PCP target ratio (3,500 to 1) (HRSA)⁵⁷ The PCP shortage variable does not take into account the need for other providers in the primary care workforce such as nurse practitioners and physician assistants.</p>
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Study Population

This study examined all primary cervical cancer cases diagnosed during the years of 2010-2014, from the United States Cancer Statistics (USCS) database, available at the National Center for Health Statistics Research Data Center.⁴⁸ The USCS database collects information on cancer incidence and survival from registries that have high quality data that represent 98% of the US population.⁴⁸ Included in the database is information on demographics (age, gender, race, and ethnicity), tumor characteristics, and geographic location (county of residence) at time of diagnosis.⁴⁸ Only those researchers with approved research plans are granted access to the database and all analyses must be conducted inside secure Federal Research Data Centers (RDCs).

All states participate in USCS registry data system database. However, five states (Kansas, Minnesota, Illinois, Michigan and Missouri) do not allow use of county of residence information for researchers in the RDC.⁴⁸ We excluded these five states and two additional states, Alaska and Hawaii, because of missing contextual data. The study sample was further restricted to include all persons having cervical cancer and excluded records: when cases were not their primary cancers and when records featured unknown cancer stage or unstaged cancer. These restrictions resulted in 59,360 individuals with cervical cancer living in 43 states during 2010 -2014.

We examined cases within the database during 2010-2014 because this time period represents the beginning of a significant time period in the US, with the implementation of the Affordable Care Act (ACA). Beginning in 2010, provisions under the ACA resulted in thousands of

individuals with pre-existing conditions obtaining health insurance through a national high-risk pool program.⁵⁸ Provisions under the ACA also resulted in millions of women gaining full coverage for CVC screening via provisions mandating coverage of preventive services without cost-sharing beginning in 2012²⁴ and millions of people obtaining health insurance via Medicaid expansion and individual health insurance marketplace subsidies beginning in 2014⁵⁹. Therefore, we expect that access to care barriers and their relationships with health outcomes during the time period 2010-2014 will considerably be different than those observed during any time period prior to 2010.

Measures

Cervical cancer cases were categorized into late stage (regional and distant) or early stage (localized, including in situ) diagnoses. We then created a dichotomous person-level late stage cervical cancer outcome variable (yes/no). In regard to study predictors, we also extracted two person-level covariates from the USCS databases⁴⁸, race or ethnicity and age. We created the race or ethnicity variable by combining USCS's race and Hispanic variables. Race or ethnicity is a recoded variable categorized into six race or ethnicity groups: non-Hispanic White, non-Hispanic Black, Hispanic, Asian Pacific, American Indian and other. The age variable is categorized into two groups: less than 50 (reference) and 50 and older.

County level variables were extracted from a number of external data sources. Data describing the percentage of individuals under age 65 with no health insurance in 2010 were obtained from the U.S. Census Bureau, SAHIE data.⁵⁰ The percent of individuals of all ages in poverty in 2010 and the proportion of population who came to the US from a different country in the prior year (2007-2011) variables were obtained from the American Community Survey (ACS).⁵² Data describing the percent of HMO penetration in 2010 was extracted from Kaiser. Data describing the population density (i.e. urbanicity) in 2010 were extracted from the Economic Resource Services (ERS) agency.⁵⁵ This measure was calculated by dividing the total population in 2010 divided by the total square miles of land area. Higher values of this measure indicate more urban places.

The county level primary care physician (PCP) shortage variable which represents number of full-time equivalent (FTE) PCPs needed in the Health Professional Shortage Area (HPSA) so

that it will achieve the population to PCP target ratio (3,500 to 1), was obtained from HRSA database.⁵⁷ The PCP shortage variable does not take into account the need for other providers in the primary care workforce such as nurse practitioners and physician assistants. The number of FQHCs and Planned Parenthood clinics were obtained from Guttmacher Institute's Contraceptive Needs and Services 2013 data report.⁵⁶ We recoded each of the three health center count variables into counts per 100,000 people by multiplying each of the counts by 100,000 and dividing the product by the total US population for each county in 2010. The primary interest of this paper is the influence of CHCs, publicly funded clinics and PCP shortages on both stage at CVC diagnosis and racial disparities in CVC diagnosis, which has never been explored. As described above, we believe the heterogeneity in these variables across counties plays a huge role in access to CVC screening and pathways to late stage CVC diagnoses and disparities.

Statistical Analysis

To examine predictors of late stage cervical cancer diagnosis we estimated two multilevel models using data from person and county levels. With persons nested within counties, we specifically used Generalized Linear Mixed Model (GzLMM) to fit two separate two-level random intercept logit model. Both models included several person and county level covariates and one cross level interaction. The models differed only in the cross-level interaction included; all other variables were the same. The first model included an interaction between race or ethnicity and PCP shortage and the second model included the interaction between race or ethnicity and the number of Planned Parenthood clinics per 100,000 people. Final random and fixed parameter estimates were calculated using Full Maximum Likelihood (FML) estimation in SAS 9.2 statistical software. We selected the multilevel model framework because it has been found to be the most efficient model for assessing correlated data or predictors at various levels simultaneously. This approach was also selected because it controls for omitted county-level effects that might bias the disparity estimates.⁴⁵ The results of these models provide us with estimates of the probability of late stage CVC given various access indicators, answering the following research questions:

- Are lower numbers of FQHCs per 100,000 people associated with increased odds of late stage for cervical cancer among women in the US, controlling for other variables?

- Does the relationship between PCP shortage and stage at cervical cancer diagnosis differ by race or ethnicity, controlling for other variables?
- Does the relationship between the number of Planned Parenthoods clinics per 100,000 people and stage at cervical cancer diagnosis differ by race or ethnicity, controlling for other variables?
- Are women of a specific race or ethnicity or age more likely to be diagnosed at a late stage for cervical cancer, controlling for other variables?
- Are higher area-level poverty, uninsured and HMO penetration rates associated with higher odds of late stage CVC among women in the US, controlling for other variables?
- Is urbanicity associated with the odds of late stage CVC among women in the US, controlling for other variables?
- Is higher area-level percent of individuals that moved from a different country associated with higher odds of late stage CVC among women in the US, controlling for other variables?

Results

Descriptive Statistics

During 2010-2014, 59,360 women were diagnosed with CVC. Approximately 61% of the CVC sample is White, 16% is Black, 17% is Hispanic, 1% is American Indian, 4% is Asian and 1% is of other race or ethnicity. The sample was also slightly older with an average age of 51 years for all CVC cases. The CVC sample also shows that 54.15% of all CVC cases diagnosed during this period were late stage diagnoses. However, Figure 1 shows that the proportion of late stage CVC diagnoses vary tremendously across counties. For example, at the county level, in 379 counties the proportion of CVC cases diagnosed at a late stage was 1 standard deviation above the county level average of 56% while the proportion of CVC cases diagnosed at a late stage CVC was 1 standard deviation below the county level average in 187 counties. Given the substantial variability in the proportion of CVC cases diagnosed at late stage across counties, we believe both person and county level factors contributed to late stage CVC incidence and disparities. **Table 2** provides the sample statistics for each of the person and county level study predictors.

On average, the county-level percent uninsured and HMO penetration was slightly high at 18.75% and 15.17%, respectively. On the other hand the average county-level percent poverty and percent of individuals that moved from a different country was lower than 1%. We also found that there were more FQHC per 100,000 people compared to PPH clinics per 100,000 people. There were approximately 2.07 FQHC per 100,000 people and less than 1 PPH clinics per 100,000 people in the US. In regards to PCP shortage, there was an average county-level need of 2.3 FTE PCP in each HPSA. Finally, we found that there was an average of 310 people per square mile across counties, indicating that counties were more rural than urban.

Multilevel Model Results

In **Table 3**, we provide the empirical results from multilevel modeling of factors at the person and county levels with county-level factors as higher levels of influence. This table reports effect estimates when no interaction term is included in the model, i.e. the base model. Examining base model results, we found that Black and Hispanic women with CVC and women with CVC who are over the age 50 were associated with higher odds of late-stage CVC compared to Whites and women under age 50. Specifically, model estimation shows that the odds of late stage CVC among Black women with CVC is 1.34 times the odds of late stage CVC among White women with CVC, controlling for all study predictors. Similarly, the odds of late stage CVC among Hispanic women with CVC is 1.10 times the odds of late stage CVC among White women with CVC, controlling for all study predictors. These findings are consistent with the current literature, demonstrating that when controlling for other study variables there are racial disparities in late stage CVC diagnoses and that being Black or Hispanic is a risk factor for late stage CVC. On the other hand, we found that the odds of late stage CVC among women with CVC who identify as “Other” race or ethnicity is 0.46 times the odds of late stage CVC among White women with CVC, controlling for all study predictors. Finally, looking at person level factors we found that the odds of late stage CVC among women with CVC who are over the age 50 is 2.70 times the odds of late stage CVC among women with CVC who are under 50, controlling for all study predictors.

At the county level, we found that the percent of the population that moved from a different country in the year prior and the number of Planned Parenthood (PPH) clinics per 100,000 people were negatively associated with stage at CVC diagnosis. Specifically, for every one clinic

increase in PPH clinics per 100,000 people, the odds of late stage CVC among women with CVC is expected to decrease by 6%, controlling for all study predictors. This suggests that counties with more PPH clinics per 100,000 people protects against late stage CVC by providing greater opportunities for healthcare services to women with CVC. In regards to the influence of immigration, we found that for every 1 percent increase in the county level percent of the population that moved from a different country, the odds of late stage CVC among women with CVC is expected to decrease by 12%, controlling for all study predictors. On the other hand, the percent of uninsured individuals and the percent of individuals in poverty were positively associated with late stage CVC diagnoses. Study results indicate that for every 1 percent increase in county level uninsured rates, the odds of late stage CVC among women with CVC is expected to increase by 1.01 folds, controlling for all study predictors. Similarly, for 1 percent increase in the county level percent of individuals in poverty, the odds of late stage CVC among women with CVC is expected to increase by 2.37 folds, controlling for all study predictors. These results suggest that counties with higher uninsured and poverty rates are risk factors for being diagnosed with CVC at a late stage.

Table 4 reports the effect estimates of the two interaction models. The estimates for the model that includes the cross-level interaction between race or ethnicity and the number of Planned Parenthood clinics per 100,000 people are under the column labeled “Interaction 1- PPH clinics*Race or Ethnicity”. The estimates for the model that includes the cross-level interaction between race or ethnicity and PCP shortage are under the column labeled “Interaction 2- PCP Shortage*Race or Ethnicity”. In the “Interaction 1- PPH clinics*Race or Ethnicity” model, we found that age less than 50 and the county-level percent of the US population that moved from a different country in the year prior were still significantly associated with lower odds of late stage CVC. Similarly, the county level percent of uninsured and percent in poverty were still significantly associated with greater odds of late stage CVC diagnosis.

Understanding the effect estimates of variables included in an interaction requires computing the marginal effects, which involves two terms – the main effect and the interaction effect. The estimates in the “Interaction 1” model further suggest that the marginal effect of PPH clinics per 100,000 people is associated with a lower probability of late stage CVC among women with CVC who are White, Black, and Other race or ethnicity. Conversely, the marginal effect of PPH

clinics per 100,000 people is associated with a higher probability of late stage CVC among women with CVC who are Asian and American Indian race and ethnicity. However, none of these interaction effects were statistically significant. The partial derivatives for these insignificant relationships are below:

$$dY/dPPH = -0.03035 + (0) \text{ (when race or ethnicity = White)} = -0.03035$$

$$dY/dPPH = -0.03035 + (-0.1686) \text{ (when race or ethnicity = Black)} = -0.1989$$

$$dY/dPPH = -0.03035 + (0.0923) \text{ (when race or ethnicity = Asian)} = 0.0619$$

$$dY/dPPH = -0.03035 + (0.3042) \text{ (when race or ethnicity = American Indian)} = 0.2738$$

$$dY/dPPH = -0.03035 + (-0.03895) \text{ (when race or ethnicity = Other)} = -0.0693$$

The interaction between Hispanic ethnicity and PPH clinics per 100,000 people was the only statistically significant interaction effect. This estimate suggests that a greater number of PPH clinics per 100,000 people is associated with a lower probability of late stage among Hispanic women with CVC.

$$dY/dPPH = -0.03035 + (-0.1534) \text{ (when or ethnicity = Hispanic)} = -0.1837$$

Estimates further suggest that for every one clinic increase in the number of PPH clinics per 100,000 people, the probability of late stage CVC among Hispanic women with CVC is expected to decrease by 0.1837. This suggests that more PPH clinics per 100,000 people is a protective factor for Hispanic women with CVC compared to that for White women.

The marginal effects of the each of the significant race or ethnicity groups are:

$$dY/Black = 0.3248 + (-0.1686)(0.2004, \text{ mean of PPH clinics per 100,000 people}) = 0.2911$$

$$dY/Hispanic = 0.1358 + (-0.1534)(0.2004, \text{ mean of PPH clinics per 100,000 people}) = 0.1051$$

$$dY/Other = -0.684 + (-0.3895)(0.2004, \text{ mean of PPH clinics per 100,000 people}) = -0.7620$$

These estimates suggest that the marginal effects of Black and Hispanic race or ethnicity are associated with higher probabilities of late stage CVC among counties with mean/average numbers of PPH clinics per 100,000 people. The marginal effect of Hispanic race or ethnicity

suggests that the probability of late stage CVC among Hispanic women with CVC is 0.1051 in counties with mean/average numbers of PPH clinics per 100,000 people. The marginal effect of Black race or ethnicity suggests that the probability of late stage CVC among Black women with CVC is 0.2911 in counties with mean/average numbers of PPH clinics per 100,000 people. On the other hand, the marginal effect of Other race or ethnicity is associated with a lower probability of late stage CVC among counties with mean/average numbers of PPH clinics per 100,000 people. The probability of late stage CVC among women of Other race or ethnicity with CVC is -0.7620 in counties with mean/average numbers of PPH clinics per 100,000 people.

In regards to the “Interaction 2- PCP Shortage*Race or Ethnicity” model, the association between the odds of late stage CVC and each of the covariates were the same in this model as they were in the “Interaction 1- PPH*Race or Ethnicity” model. Specifically, race or ethnicity, age less than 50, area-level percent of individuals that moved from a different country and area-level poverty, uninsured rates were statistically significantly associated with the odds of late stage CVC among women with CVC in the US. However, we found no statistically significant interaction effects between race or ethnicity and PCP shortage.

Discussion

Current literature suggests that access to health care is impacted by factors at various levels, yet most of the studies investigating late stage CVC and disparities have examined factors occurring strictly at the individual level.⁴²⁻⁴⁴ However, we found that there is extreme variability in the proportion of late stage CVC cases across counties (**Figure 1**), which suggests there may be county level factors influencing stage at diagnosis among women with CVC. Thus, we add to the literature by assessing access to care barriers occurring at the county level while accounting for some consistently identified individual level factors associated with late stage CVC as well. Given the increased need for primary care physicians²⁸ and uninsured populations²⁷ we further narrowed our focus to the influence of availability and affordability related indicators of access to care. Ultimately, our study goals were to identify the access to care barriers associated with late stage diagnosis and determine how the relationship between these barriers and stage at CVC diagnosis differed by race or ethnicity. We found that area-level percent in poverty, percent uninsured and percent that moved from a different country and Planned Parenthood clinics per

100,000 people were each associated with late stage CVC diagnosis. However, primary care physician shortage areas were not a significant predictor of late stage CVC.

While poverty and uninsured status have previously been identified in the literature as individual level risk factors for late stage CVC diagnosis, to our knowledge this is the first time they have been identified as significant county level risk factor for late stage CVC. This suggests that not only are individual socioeconomic status (SES) and insurance status risk factors for late stage CVC diagnosis but that the average SES and percent insured among the county in which a woman lives is also a risk factor for late stage CVC diagnosis. This highlights the need for more county-wide interventions and policy reforms to increase CVC screening rates by developing more affordable or free screening solutions and helping individuals to overcome barriers to health care coverage. This also highlights the need to develop and implement multilevel interventions to address barriers to screening access that occur not only at the individual level but the community, health care service, and policy levels as well. Many researchers have shown that when an ecological model-based approach is used to develop intervention strategies that target multiple levels, we are most likely to achieve substantial and sustained change.⁶⁰⁻⁶³

Findings regarding the influence of county level percent poverty and percent uninsured further highlight that lack of health insurance coverage and poverty are important access barriers associated with stage at CVC diagnosis. This discovery suggests that there is a need to identify and determine the magnitude of the effects of those factors likely working to circumvent the protective effects of the provisions under the ACA. For example, commercial health insurance inside and outside of the health exchanges are exempt from the ‘no cost sharing’ feature of the preventive services provision under the ACA when preventive services are not delivered by a network provider.⁶⁴ Similarly, private health plans that existed prior to March 23, 2010 were considered to be ‘grandfathered plans’ and were exempt from required coverage for preventive services under the ACA, including CVC screening.⁶⁵ It is likely that as a result of both of these loopholes, large proportions of various populations remained in a position where they were unable to afford healthcare. Thus, these loopholes may explain why area-level percent poverty (i.e. affordability) is still a barrier associated with stage a CVC diagnosis during 2010-2014. Ultimately, these loopholes and other ACA opposing factors such as non-Medicaid expansion

states should be investigated to determine the impact they have on access to CVC screening and stage at diagnosis. These findings could likely highlight the need for further health policy reform.

Unlike area-level percent poverty and percent uninsured indicators, the relationship between Planned Parenthood clinics per 100,000 people and late stage CVC has never been explored. However, the number and distribution of these clinics reflects availability of primary care providers and affordability of women health services such as CVC screening as these clinics provide services at low or no cost. Thus, we were not surprised to find that counties with more PPH clinics per 100,000 people were associated with decreased odds of late stage CVC among women with CVC. Although there is continued political controversy related to PPH clinics because of their provision of abortion care⁶⁶ their importance in providing CVC screening services and reducing the likelihood of late stage CVC cancers is clearly demonstrated in this study. These results are of extreme relevance, as Planned Parenthood announced that they would voluntarily withdraw from Title X federal family funding programs, which provides PPH with nearly \$60 million annually, rather than comply with new laws that forbids referrals to doctors who can perform abortions.⁶⁶ Based on our results, it is our hypothesis that a significant lost in funding would restrict access to PPH clinics CVC screening services and thus impose a greater burden of late stage CVC, specifically among Hispanic women.

We were also not surprised to find that among the racial disparities we identified in this study, a higher number of PPH clinics per 100,000 people were significantly associated with lower odds of late stage CVC among Hispanic women. Planned Parenthood clinics provide services to more than 560,000 Latina patients each year.⁶⁷ We believe PPH clinics large Latina service population and the protective effect identified in this study is likely the result of PPH clinics highly publicized commitment to provide affordable primary and preventive services to all regardless of factors including immigration status.⁶⁸ The second likely explanation for this protective effect is that PPH clinic led groups have implemented several effective interventions aimed at increasing CVC screening among Hispanic women across the US. For example, the local chapter of Planned Parenthood of Wisconsin led a successful community-based intervention called *Cuidándome* that aimed to increase cervical and breast cancer screening among low-acculturated Latinas in Dane County, Wisconsin.⁶⁹ It is likely that similar PPH clinic led interventions exist across the US and that they have been successful in preventing late stage CVC among Hispanic

women by increasing access to screening services. In fact, a map of PPH clinic Latinx Advocacy Programs shows that these programs are active in 19 states including: Arizona, California, Colorado, Connecticut, Florida, Illinois, Massachusetts, Minnesota, New Mexico, New York, Nevada, Pennsylvania, Rhode Island, Tennessee, Texas, Utah, Virginia, Washington, and Wisconsin.⁶⁷

The final possible explanation for the observed protective effect is that there are effective measures in place for increasing the intent to screen for CVC among Hispanic women and PPH clinics are the most proximal clinics to most Hispanic populations. **Figure 2** shows that Hispanic women are heavily concentrated in counties within Texas, New Mexico, Arizona, California, Colorado and Idaho. Similarly, **Figure 3** shows that the number of PPH clinics per 100,000 people is highest within counties in Texas, Colorado, Arizona, California, Iowa and Washington. Thus, we believe it could be the overlap in the distribution of Hispanic women and PPH clinics geographically that allow Hispanic women to benefit most from PPH clinic services. Based on **Figure 4**, we also believe that those 7 counties colored black in both Texas and Colorado are the main forces driving the observed protective effect. These places represent those counties that have both the largest proportion of Hispanic women with CVC and the highest number of Planned Parenthood clinics per 100,000 people compared to other counties, representing places where Hispanic women are most benefitting the PPH clinic screening services. Overall, mapping results suggest that if there was a more random spread of PPH clinics across geography racial disparities in late stage CVC among Hispanics and other minority groups serviced by PPH clinics could also be potentially reduced.

While we were not surprised to find that Hispanic women were disproportionately burdened by late stage CVC or that this disparity could be partially explained by an access barrier, we were surprised to find that higher immigration rates were associated with lower odds of late stage CVC. Given that the existing literature has consistently found that Hispanic women are associated with greater odds of late stage CVC^{3-4, 49} and that Hispanics are the largest immigrant population in the US⁷⁰, we expected that higher county-level percentages of the US population that moved from a different country during the prior year would be associated with higher odds of late stage CVC. However, previous research among 32 US immigrant groups found that nearly all immigrants were more educated than those who remained in their home countries⁷¹ and

other findings suggests that higher education levels are associated with higher cervical cancer screening rates.⁷² Thus, it is plausible that educational selectivity in US immigration likely explains the observed relationship between higher percentages of the US population that moved from a different country during the prior year and lower odds of late stage CVC diagnosis.

On the other hand, this finding could indicate that the majority of the immigrant population represented with this variable during 2007-2011 may have come from countries with effective Pap screening interventions. If these individuals came from countries with heavily implemented screening programs, which could have focused on education, affordability or accessibility, it would explain why higher county-level percentages of the US population that moved from a different country during the prior year would be associated with higher odds of late stage CVC. However, additional research is needed to better understand this relationship. Overall, this study demonstrates that there are still significant access barriers associated with the odds of late stage CVC among women in the US and that these barriers can occur beyond the individual level. This suggests that by the time period 2010-2014 there is still a need to develop strategies for improving availability and affordability of health care services including CVC screening. This further highlights the importance of assessing multiple levels of influence to develop a comprehensive understanding of the problem and the pathway to these problems. Additional research is needed to determine whether access to care barriers at the state level may also play a role in stage at CVC diagnosis. Research is also needed to further explore multilevel factors associated with late stage CVC among Black women and women over the age of 50 as they were found to be disproportionately affected. The odds of late stage CVC among Black women was not significantly associated with the two access to care indicators tested in this study, PCP shortage and PPH clinics per 100,000 people. However, study results have indicated that access to care is still a significant predictor of stage at CVC diagnosis. Thus, it is essential to continue to explore the relationship between racial disparities in stage at CVC diagnosis and access to care barriers that may occur at other levels of influence. Further identifying the multilevel factors associated with late stage diagnosis and disparities is essential as CVC stage at diagnosis plays a significant role in cervical cancer treatment, prognosis and survival.⁷³ Failing to address the identified access to care barriers and investigate relationships that remain unclear will result in continued high CVC mortality rates and persistent racial disparities in these outcomes.

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Figure 1

The Proportion of Late Stage Cervical Cancer Across Counties during 2010-2014
(Standard Deviation Map)

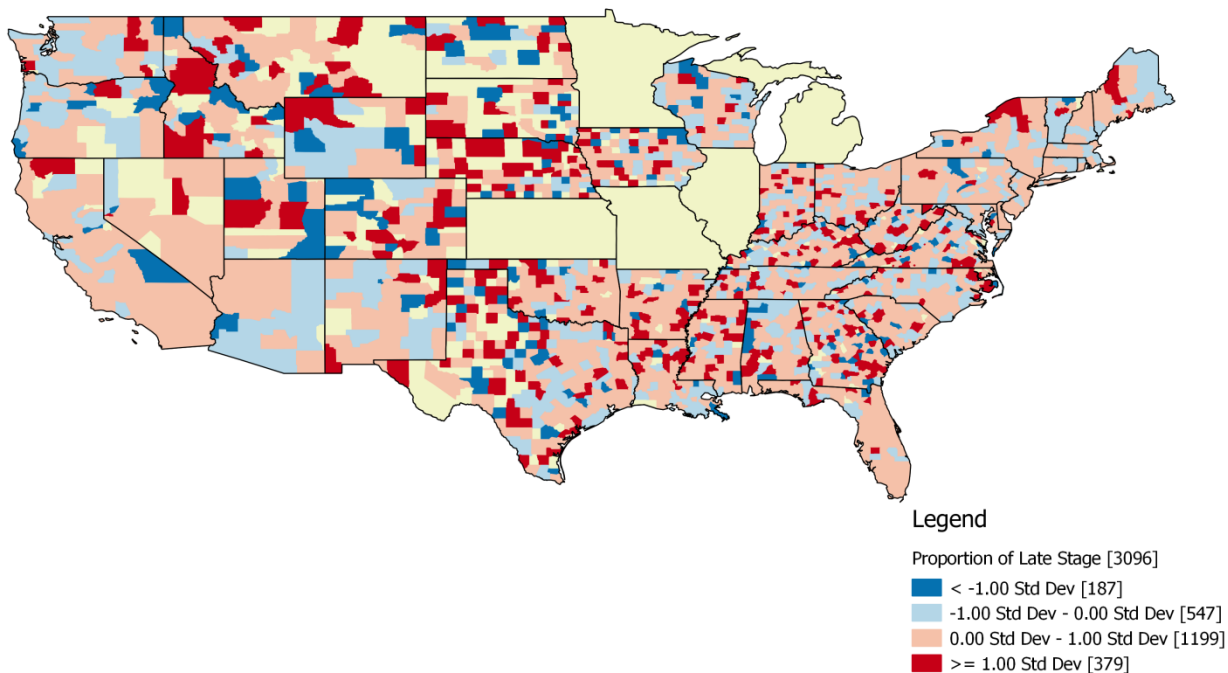


Table 2: Descriptive Statistics

Variable Name	Mean or percent	Standard deviation	Minimum and maximum values
Person compositional Variable (n=59,360)			
Late Stage CVC Diagnosis			
0	30184(50.85%)	NA, binary	NA, binary
1	29176(54.15%)	variable	variable
Race or Ethnicity			
0 non-Hispanic White (ref)	36116(60.84%)	NA, categorical	NA,
1 non-Hispanic Black	9229(15.55%)	variable	categorical
2 Asian	2615 (4.41%)		variable
3 American Indian	538 (0.91%)		
4 Hispanic	10193(17.17)		
5 Other	669(1.13%)		
Age <-50			
0	30184(50.85%)	NA, binary	NA, binary
1	29176(49.15%)	variable	variable
Age	51.3679245	15.2647831	-
County contextual Variable (n=2,357)			
Percent Moved From Different Country	0.320	0.420	0, 7.34
Percent HMO Penetration	15.1734	9.4779	1.7114, 42.087
Percent Uninsured	18.7532	5.4156	3.60, 41.40
Percent Poverty	16.40	6.48	3.44, 53.49
FQHCs per 100,000 people	2.0748	4.8789	0,100.35
PPH clinics per 100,000 people	0.2004	0.7267	0, 9.344
PCP-shortage	2.3211	3.5861	-11.57*, 35.15
Urbanicity=pop10/land	310.4118	1971.6079	0, 69178.9916

*A maximum county-level PCP shortage of 35.15 indicates that there is a need for roughly 35 additional full-time equivalent (FTE) PCPs in a Health Professional Shortage Area (HPSA) in order to achieve the population to PCP target ratio (3,500 to 1). Similarly a minimum county-level PCP shortage of -11.57 indicates that there are roughly 12 more FTE PCPs in a HSPA than what is needed to achieve the population to PCP target ratio (3,500 to 1).

Table 3 : Multilevel Model Results without Interactions - Base Model

Covariate	Coefficient	Error	p-value
Person compositional variable			
Intercept	0.4331	0.05657	<.0001
Race or Ethnicity			
0 non-Hispanic White (ref)	0	-	-
1 non-Hispanic Black	0.2906	0.02866	<.0001
2 Asian	0.06239	0.04745	0.1886
3 American Indian	0.1532	0.1001	0.1257
4 Hispanic	0.09638	0.02826	0.0006
5 Other	-0.7800	0.1159	<.0001
Age < 50			
0 (ref)	0	-	-
1	-0.9933	0.01909	<.0001
County contextual variable			
Percent Poverty	0.8642	0.2672	0.0012
Percent HMO Penetration	0.000917	0.001185	0.4390
Percent Uninsured	0.006774	0.002611	0.0095
Percent Moved From Different Country	-0.118428	0.031861	0.0002
Urbanicity=pop10/land	-2.98E-7	2.242E-6	0.8942
FQHCs per 100,000 people	-0.00218	0.005525	0.6927
PPH clinics per 100,000 people	-0.05681	0.02820	0.0439
PCP shortage	-0.00045	0.002007	0.8225
Variance Components (county level)			
	0.01736	0.005097	-

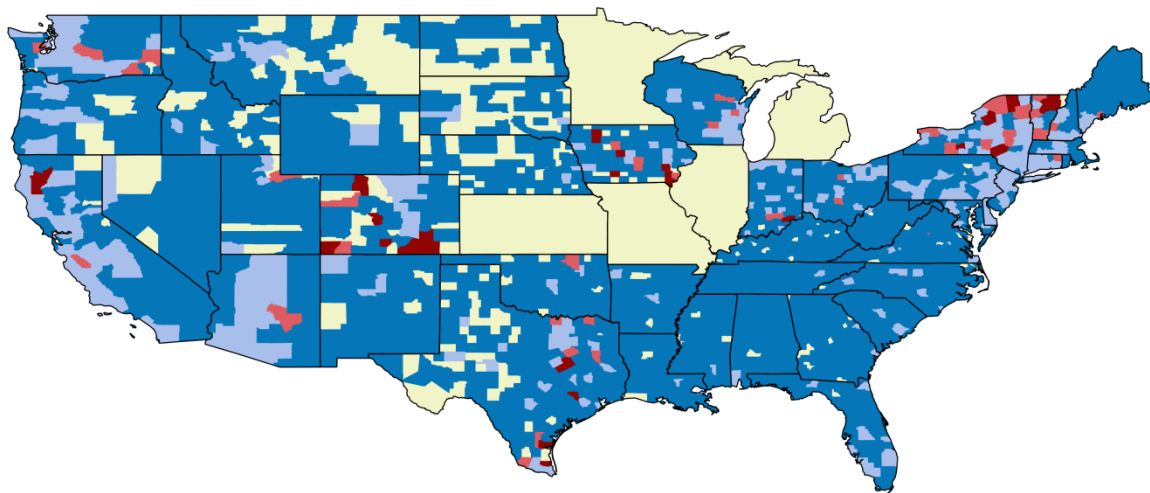
Table 4 : Multilevel Model Results with Interactions

Covariate	Interaction 1 –PPH*Race or Ethnicity			Interaction 2- PCP Shortage*Race or Ethnicity		
	Coefficient	Error	p-value	Coefficient	Error	p-value
Person compositional variable						
Intercept	0.4247	0.05652	<.0001	0.4382	0.05655	<.0001
Race or Ethnicity						
0 non-Hispanic White (ref)	0	-	-	0	-	-
1 non-Hispanic Black	0.3248	0.03523	<.0001	0.2668	0.03842	<.0001
2 Asian	0.04221	0.06702	0.5288	0.06328	0.07169	0.3774
3 American Indian	0.06837	0.1245	0.583	0.1768	0.1345	0.1888
4 Hispanic	0.1358	0.03513	0.0001	0.1055	0.03977	0.008
5 Other	-0.684	0.1559	<.0001	-0.8264	0.1553	<.0001
Age < 50						
0 (ref)	0	-	-	0	-	-
1	-0.993	0.01909	<.0001	-0.9937	0.01909	<.0001
County contextual Variable						
Percent Poverty	0.9258	0.2621	0.0004	0.909	0.2623	0.0005
Percent HMO Penetration	0.000894	0.001181	0.4491	0.00085	0.001186	0.4733
Percent Uninsured	0.006852	0.002604	0.0085	0.006697	0.002618	0.0105
Percent Moved From Different Country	-0.121426	0.031614	0.0001	-0.120177	0.031785	0.0002
Urbanicity=pop10/land	-4.09E-07	2.23E-06	0.8546	-4.31E-07	2.26E-06	0.8489
FQHCs per 100,000 people	-0.00132	0.005191	0.7992	-0.00094	0.005195	0.8558
PPH clinics per 100,000 people	-0.03035	0.03139	0.3336	-0.05897	0.02812	0.0360
PCP shortage	-0.00087	0.001978	0.6614	-0.00101	0.002357	0.6674
Race* PPH clinics per 100,00 capita						
0 non-Hispanic White (ref)	0	-	-			
1 non-Hispanic Black	-0.1686	0.102	0.0982			
2 Asian	0.09233	0.1907	0.6283			
3 American Indian	0.3042	0.2684	0.2571			
4 Hispanic	-0.1534	0.07961	0.0531			
5 Other	-0.3895	0.4352	0.3708			

Race* PCP Shortage						
0 non-Hispanic White (ref)				0	-	-
1 non-Hispanic Black				0.003085	0.003594	0.3907
2 Asian				0.000155	0.005745	0.9784
3 American Indian				-0.00454	0.01864	0.8074
4 Hispanic				-0.00083	0.003352	0.8051
5 Other				0.006918	0.01521	0.6492
<hr/>						
Variance Components (county level)	0.01692	0.005097	-	0.01755	0.005098	-
<hr/>						

Figure 2

Planned Parenthood Centers Per County Capita



Legend

- Per Capita PPH [2328]
- < 0.00 Std Dev [1957]
 - 0.00 Std Dev - 2.00 Std Dev [294]
 - 2.00 Std Dev - 4.00 Std Dev [45]
 - >4.00 Std Dev [30]

Figure 3

**Percent of Hispanic Women with CVC Across Counties in the U.S.
(Standard Deviation Map)**

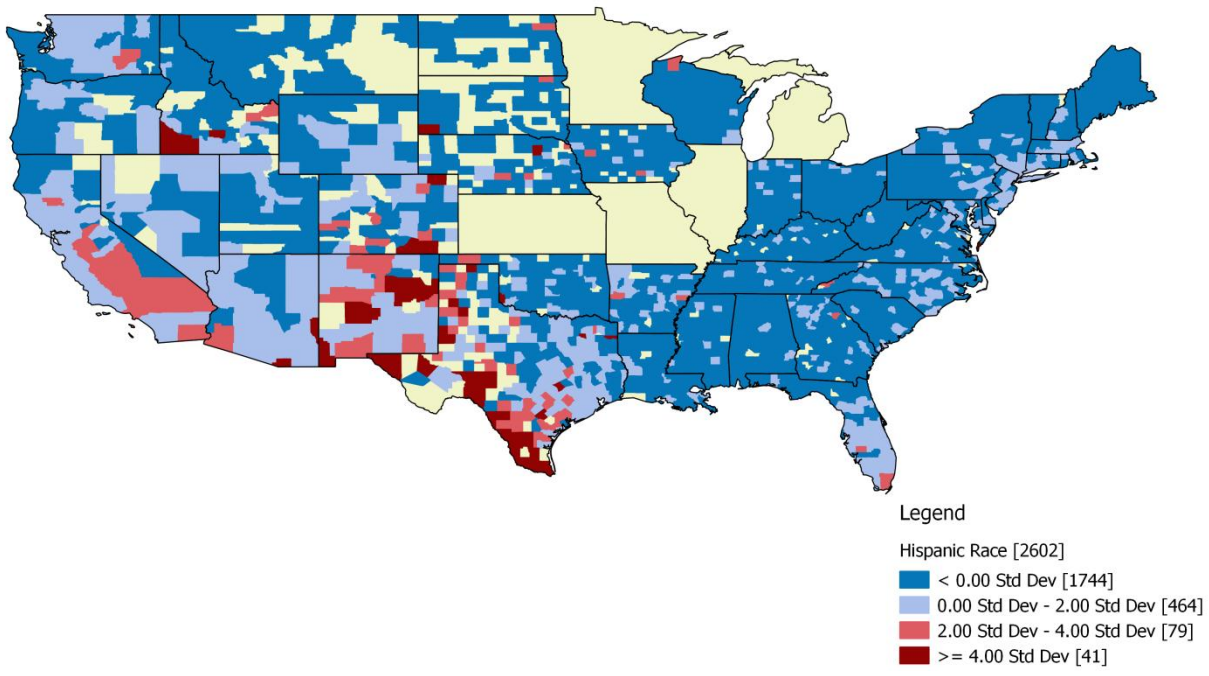
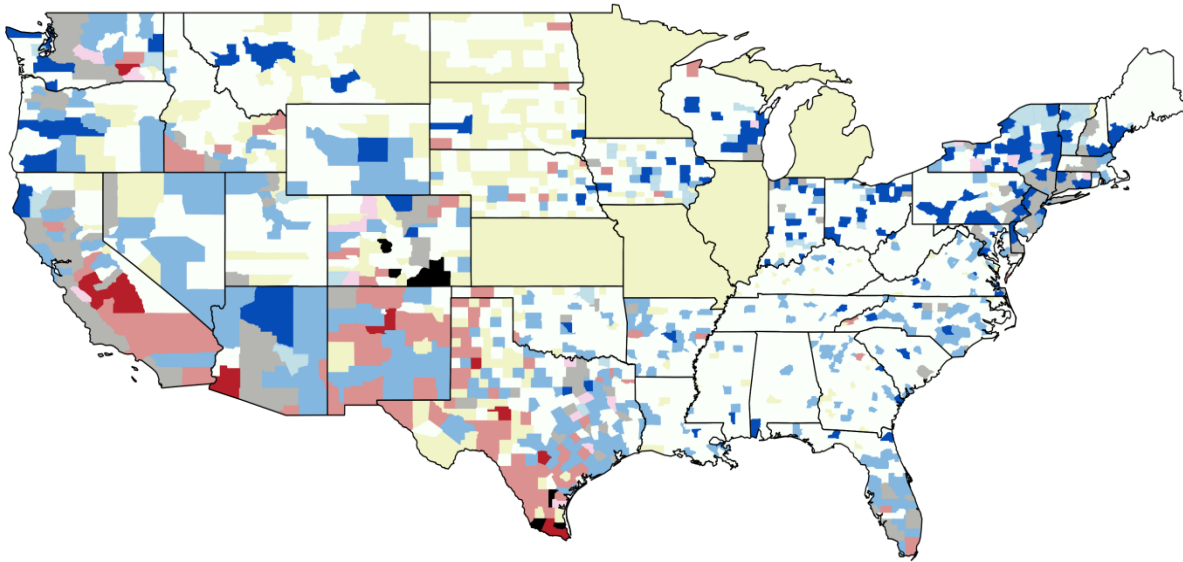


Figure 4

Bivariate Map of Planned Parenthood Clinics per 100,000 people and Percent of Hispanic Women with CVC in the U.S.



Legend of Bivariate Categories

(Number of Counties in Each Category Included)

Percent of Hispanic Women

<0SD 0-2SD 2-4+SD

	<0SD	0-2SD	2-4+SD
<0SD	1564	316	105
0-2SD	149	134	12
2-4+SD	50	19	7

Planned Parenthood Clinics
per 100,000 people

Chapter Four: Multilevel Access Barriers Influencing Geographic Disparities in Late Stage Cervical Cancer among Counties in the U.S.

Introduction

Due to early detection of precancerous cervical cell changes and early stage cancers via Pap testing, cervical cancer (CVC) is one of the most preventable cancers in the US.¹ However, more than 50% of women with CVC in the US are diagnosed at a late stage (regional or distant).² Specifically, the Surveillance, Epidemiology, and End Results (SEER) program indicates that 36% of the CVC cases were diagnosed at regional stage and 15% at distant stage.² Regional and distant stage CVC diagnoses are associated with poor prognosis, increased morbidity and lower 5-year survival rates.³ In fact, the 5-year survival rate for localized cervical cancer is 91.7%, compared to a 5 year survival rate of 56% for regional cervical cancer and 17% for distant cervical cancer.²

Existing literature suggests that the burden of late stage CVC is unequally distributed among people and places in the US.⁴⁻⁵ Late stage CVC has been found to disproportionately burden African American⁴⁻⁵ and Hispanic⁴ women and women who are over the age of 50.⁴ Foreign born women⁶, women without health insurance⁷ and women with lower incomes⁸ have also been found to be disproportionately burdened by late stage CVC. Previous research further suggests that disparities in late stage CVC incidence exist between different geographic populations.^{4,9-11} According to a 2013 study investigating late stage CVC in Central Appalachia, there was significant variability in the incidence of late stage CVC across counties in the state of Ohio.⁹ A later 2014 study found that there was significant variability in stage at CVC diagnosis among 4,388 census tracts in the state of Texas (TX).¹⁰ Major findings from this study indicate that clusters with statistically significantly increased risk for late stage CVC were located in the Western tip of TX, Southern TX, the Bryan/College State area and central Houston.¹⁰ A third geographic disparities study also found considerable differences in late stage CVC incidence among census tracts within the state of New Jersey (NJ).¹¹ Specifically, this study identified three significant late stage CVC high incidence areas in: northeastern NJ, central NJ and Southwestern NJ.¹¹

Identifying the factors associated with geographic variability in stage at CVC diagnosis is an essential approach to strategically targeting places in need of CVC prevention and control. However, research that aims to answer questions related to *where* there is a need for intervention, requires an ecological approach that uses groups rather than individuals as the unit of study. Previous ecological studies have found that a number of compositional and contextual factors are associated with CVC screening and stage at diagnosis.¹²⁻¹⁷ Among these factors are area level socioeconomic status (SES)^{10, 12} and community-level age, race and immigrant composition.^{10,13} Studies have also shown that contextual factors impacting access to care are associated with CVC screening and stage at diagnosis.^{10,14-16} Specifically, the literature suggests that health services resources in the community, travel time to the nearest screening facilities and availability of services in the community represent contextual access to care factors associated with CVC screening and stage at diagnosis.^{10, 14-16}

Although several compositional and contextual factors influencing CVC screening and stage at CVC diagnosis have been documented, there are still a number of gaps in the existing literature. First, no study has described the county-level variation in stage at CVC diagnosis for nearly the total US (n=43 states). In fact, many of the investigations of geographic disparities in screening and stage at diagnosis have been limited to a single state or performed at the census tract level.⁹⁻¹¹ Second, because previous studies have been limited to a single state, no study has identified the contextual factors that may help to explain the variation in late stage CVC that potentially exists among all counties in the US. Third, in regards to research aimed at identifying factors associated with screening and stage at CVC diagnosis a number of contextual access to care factors have been unexplored, including health policies.

Recent studies suggest that the most significant predictor of late stage CVC is whether or not a woman has had a Pap test in the past 3 years (i.e. current screening), which is largely attributed to access to care.^{5,17-19} However, access to CVC screening has been consistently found to be unequal across various populations in the US.²⁰ The observed variability in access to CVC screening across populations thus highlights the importance of focusing on contextual access to care in order to explain the geographic variability in late stage CVC. The persistent variability in access to care across populations over time also highlights the need to focus on those contextual access to care factors that have been less commonly explored, including health policies.^{12, 21}

Given the limitations in the existing literature, this study aims to 1) identify county-level disparities in late stage CVC across (n=43 states) and 2) explain the observed disparities by identifying statistically significant ecological relationships between high proportions of late stage CVC diagnoses in counties and several county and state-level variables. Using a hybrid model that draws from the Access to Care Framework²² Theory of Access²³ and Socio-ecological model²⁴, we specifically explore the relationships between late stage CVC and several indicators of access to CVC screening. Among the study variables we are most interested in are unexplored access to care factors that are determined by state policy including: state policies regarding scope of practice for nurse practitioners, state healthcare insurance CVC screening mandates and state-level proportions of individuals enrolled in self-insured employer-sponsored insurance plans. Each of these three state-level variables is described further below.

Nurse Practitioner Regulations

Nurse practitioners (NPs) are advanced practice registered nurses (APRN) that provide quality care, yet receive training and enter the healthcare system in less time than their physician colleagues.²⁵ According to the American Academy of Nurse Practitioners, there are approximately 140,000 NPs in the US²⁶ with over 50% of the NP workforce practicing in primary care settings.²⁷

Because NPs play such an important role in primary care, they have also been found to play a substantial role in providing cervical cancer screening tests.²⁸ A recent systematic review found that among 5 studies evaluating the role of NPs in Pap testing, 72%-98% of APRNs reported that they routinely provided or recommended Pap tests to patients.²⁹ This review also found that in most studies physicians reported being amenable to APRNs conducting Pap tests.²⁹ Overall, the incorporation of NPs into the healthcare delivery system has increased overall access to healthcare³⁰ and has also been associated with reaching previously unscreened and under-screened women at risk for cervical cancer.²⁶

Despite the known benefits of having NPs in the healthcare delivery system, there are several barriers that prevent them from being fully deployed. Among those barriers are state-based regulations governing NP scope of practice. These regulations can restrict or prevent NPs from practicing to their full potential. While some states allow NPs full scope of practice, including

the ability to evaluate, diagnose, treat, and prescribe under the exclusive licensure authority of the state board of nursing, others impose restrictions, requiring supervision, delegation, or team management by a physician in order to provide patient care, and limiting engagement in at least one element of practice.³¹ Recent data indicate that 22 states and the District of Columbia allow NPs full scope of practice and 29 states impose restrictions on their practice.³¹

Many argue that complying with restrictive scope of practice laws could take time from both NPs and their supervising physicians³² and limit the supply of health services.³³ We hypothesize that states with restrictive NP scope of practice laws are associated with poorer access to quality care and consequently higher proportions of late stage cervical diagnoses.

Cervical Cancer Screening Mandates & Self-Insured Plans

Since the early 1960s, requirements regarding coverage provisions of private health insurance policies has largely fallen under the jurisdiction of state governments.³⁴ Mandated state insurance coverage requirements were established in efforts to promote public health and improve access and treatment for people with specific diseases, including cancer.³⁴ State cancer mandates now include requirements for screening, prevention and treatment. In 2009, there were approximately 25 cancer-related insurance mandates across states.³⁴ Among those mandates, only two focused specifically on cervical cancer: required cervical cancer screening and Human Papillomavirus (HPV) vaccination. In regard to required cervical cancer screening mandates, there is significant variation across states. By 2009, thirty-two states and the District of Columbia required insurers to cover cervical cancer screening while 19 did not.³⁴

While state CVC screening mandates are now perhaps less important, following the implementation of new preventive services coverage provisions under the Affordable Care Act (ACA) from 2012-2014, there are still reasons to expect that they may be significant predictors in the models estimated here. First, they established a stronger baseline in states that adopted them prior to 2010 that was absent in other states. Thus, these states were poised to perform better than states who saw these requirements for the first time in 2010. Several other factors suggest the importance of state mandates in supporting access to healthcare.³⁵⁻³⁸ For example, private health plans that existed prior to March 23, 2010 were considered ‘grandfathered plans’ and were exempt from required coverage for preventive services under the ACA, including CVC

screening.³⁶ Similarly, commercial health insurance inside and outside of the health insurance exchanges are exempt from the ‘no cost sharing’ feature of the preventive services provisions under the ACA when preventive services are not delivered by a network provider.³⁷ These types of loopholes reduced the potential for federal ACA mandates to achieve their intended effects on access to healthcare by exempting large portions of the insured population. Furthermore, a systematic review of studies investigating the ACA’s impact on cancer screening and diagnosis found that the impact on changes in screening in the general population was mixed.³⁸ Together these loopholes and findings suggest that state mandates may still play a significant role in access to healthcare post-ACA implementation in 2010.

In 2013, Miles-Richardson et al. examined the impact of state cervical cancer screening mandates on screening rates and racial disparities in screening rates among women in Georgia, North Carolina and South Carolina and found no significant effects.³⁹ However, a later 2017 study found that Pap test mandates increased past-2-year screening rates by 1.3 percent. Additional results from this study suggest that the effects of the mandate on screening rates were significantly larger among Hispanic women.⁴⁰

We believe findings suggesting a relationship between CVC screening and state cancer-related insurance mandates have been inconsistent because there may be significant lags in effects, so later studies may find larger effects. Also, studies have not considered important contingencies related to private sponsorship of self-insured plans, although these plans account for more than 50% of persons with employer-sponsored health insurance.⁴¹ According to provisions under the Employee Retirement Income Security Act (ERISA), private employer self-funded plans are exempt from most state insurance laws, including mandated benefits.⁴² However, self-funded plans established by public employers are not exempt from state insurance laws.⁴² Thus the effects of these state mandates may depend upon how much of the self-insured population is in public or private plans.

We hypothesize that states with CVC screening mandates are associated with lower county-level proportions of late stage CVC compared to states without these mandates. However, we hypothesize that this relationship will also be impacted by the percentage of the state population in private self-insured plans, as these plans can avoid the protective effect of mandates. Therefore, we hypothesize that higher proportions of the state population in private self-insured

plans will be associated with higher proportions of late stage CVC in places with and without state CVC screening mandates. Yet, because this relationship has never been explored, we are uncertain whether the effect of this barrier will be greatest in places with or without mandates. However, understanding this relationship is essential as the number of private self-insured plans has increased over time. We are not able to control separately for employees in private versus public self-insured plans, however our data include all individuals in private self-insured plans.⁴³

Conceptual Model

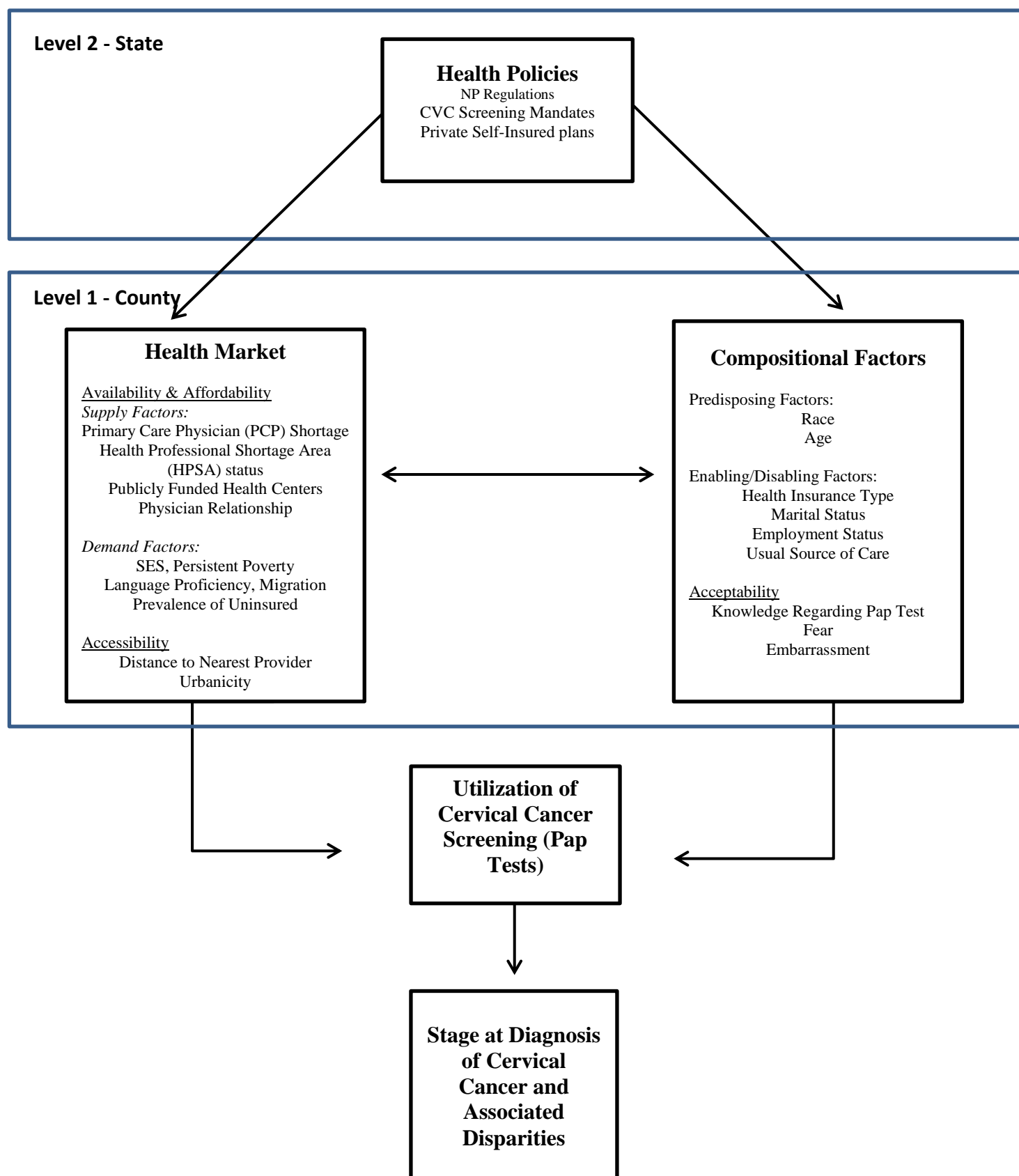
As previously stated, the most significant predictor of late stage CVC is whether or not a woman has had a Pap test in the past 3 years (i.e. current screening), which is largely attributed to access to care.^{5,17-19} However, access to CVC screening has been consistently found to be unequal across various populations in the US.²⁰ Given the significance of access to CVC screening in the etiological pathway to late stage diagnosis, it is critical to identify factors contributing to unequal access to CVC screening (i.e. access to screening barriers) to better understand stage at CVC diagnosis outcomes.

Based on the existing literature, we know that unequal access to cervical cancer screening and late stage CVC diagnosis are both influenced by complex and interacting social, environmental and behavioral processes that occur at varying geographical and socioecological levels.⁴⁴ However, current research investigating disparities in stage at cervical cancer diagnosis and access to CVC screening has not focused on the simultaneous effects of factors occurring at multiple geographical and socioecological levels. In fact, a review of the literature indicates that most of the studies on this topic limit their investigations to one level of influence at a time, with individuals being the most common socioecological level and census tract being the most common geographical level.⁴⁴⁻⁴⁸ Thus, we do not have knowledge of the effects of several factors that lie at the health policy level and we do not know whether the effects of previously studied variables hold true when accounting for significant factors that lie at other geographic scales/levels. This is important because failing to account for multilevel factors and compositional characteristics of the study population - which helps control for migratory population selection effects - has been found to significantly bias regression estimates.⁴⁹

To address the concerns raised in the recent literature and achieve reliable estimates, we developed a multilevel conceptual model for understanding access to CVC screening and late stage CVC outcomes by drawing from the current literature, the socio-ecological²⁴ model and both Aday and Andersen's 1974 Access Framework²² and Penchansky and Thomas's 1981 Theory of Access.^{23,50} This hybrid model describes the influence and spatial interactions among two geographical and socioecological levels. Level 2 represents the policy level of the socio-ecological model and includes health policy factors that vary across states. Level 1 represents both the community and institutional levels of the socio-ecological model and includes compositional and contextual factors that vary across counties. The compositional factors included in the model were mostly selected to represent what Aday and Andersen define as predisposing and enabling characteristics of the population at risk. The contextual factors included were selected to reflect what Penchansky and Thomas define as availability, affordability and accessibility factors. Each of the variables in the model have been found or are hypothesized to influence stage at CVC diagnosis. However, more aspects are listed than can be modeled using currently available data or computing power. We describe the specific variables used and a rationale for using them in the methods section below.

Ultimately, it is our hypothesis that there are significant county-level disparities in late stage CVC diagnosis. It is also our hypothesis that these geographical disparities can be explained by several unexplored access to care barriers that vary based on place. Identifying the factors associated with geographic variability in stage at CVC diagnosis is an essential approach to strategically targeting places in need of CVC prevention and control. It is also essential for informing health policy aimed at improving access to care and developing community-level interventions. To our knowledge, this will be the first study to use multilevel modeling to understand multilevel CVC screening access barriers and their effects on late stage CVC diagnosis.

Figure 1: Model of Cross-Level Interactions Influencing CVC Stage at Diagnosis and Disparities



Methods

Study Population

This study examined all primary cervical cancer cases diagnosed during the years of 2010-2014, from the United States Cancer Statistics (USCS) database, available at the National Center for Health Statistics Research Data Center.⁵¹ This database collects information on cancer incidence and survival from registries that have high quality data representing 98% of the US population.⁵¹ Included in the database is information on demographics (age, gender, race, and ethnicity), tumor characteristics, and geographic location (county of residence) at time of diagnosis.⁵¹ Only those researchers with approved research plans are granted access to the database and all analyses must be conducted inside secure Federal Research Data Centers (RDCs).

All states participate in USCS registry data system database. However, five states (Kansas, Illinois, Michigan, Minnesota and Missouri) did not allow us to use county of residence information.⁵¹ We excluded these five states and two additional states, Alaska and Hawaii, because of missing contextual data. The study sample was further restricted to include all persons having cervical cancer and excluded records when this was not their primary cancer or when records showed unknown cancer stage or unstaged cancer. These restrictions resulted in 59,360 individuals diagnosed with cervical cancer living in 43 states during 2010-2014.

We examined cases within the database during 2010-2014 because this time period represents the beginning of a significant time period in the US, with the implementation of the Affordable Care Act (ACA). Beginning in 2010, provisions under the ACA resulted in thousands of individuals with pre-existing conditions obtaining health insurance through a national high-risk pool program.⁵² Provisions under the ACA also resulted in millions of women gaining full coverage for CVC screening via provisions mandating coverage of preventive services without cost-sharing beginning in 2012 and millions of people obtaining health insurance via Medicaid expansion and individual health insurance marketplace subsidies beginning in 2014.⁵³

Therefore, we expect that access to care barriers and their relationships with health outcomes during the time period 2010-2014 will considerably be different than those observed during any time period prior to 2010.

Outcome Variable

Cervical cancer cases were categorized into late stage (regional and distant) or early stage (localized, including in situ) diagnosis. We then created a county-level proportion of late stage diagnoses variable. This variable aggregated the total number of late stage cases within each county by Federal Information Processing Standard (FIPS) code and divided this by the total number of CVC cases within each county. The overall county-level proportion of CVC case diagnoses at late stage during the study period is .556 or 56%.

County-Level Explanatory Variables

In regard to compositional study predictors, we extracted two person-level covariates from the USCS database and aggregated them to the county-level: race or ethnicity and age. Combining USCS's race and Hispanic variables we created six race or ethnicity variables describing the percent of women in each county who are: non-Hispanic White, non-Hispanic Black, Hispanic, Asian Pacific, American Indian or other. According to the current literature, Black and Hispanic women have the highest incidence of CVC, are significantly less likely to be screened for CVC, and are more likely to be diagnosed at a late stage.⁴⁻⁵ Therefore, we account for this demographic composition in our model because we expect that places with higher proportions of women with CVC who are Black or Hispanic will be associated with higher proportions of late stage CVC. The age variable represents the proportions of women with CVC who are age less than 50. According to the literature, older women and women over the age of 50 are significantly more likely to be diagnosed at a late stage.^{4,7} Therefore, we control for this demographic composition in our model because we expect that places with higher proportions of women with CVC who are age less than 50 will be associated with lower proportions of late stage CVC.

Other county-level contextual variables were extracted from a number of external data sources. The percent of the general population ages 18-64 that speak English poorly (2007-2011) variable was obtained from the American Community Survey (ACS).⁵⁴ The literature suggests that Hispanic and foreign-born women have greater odds of late stage CVC.^{4,6} The literature also suggests that recent immigration status and poor language proficiency are significant barriers to CVC screening among Hispanic populations.⁵⁵⁻⁵⁶ Therefore, we control for this variable in our model because we also expect that places with a higher percent of the population ages 18-64 that speaks English poorly will be associated with higher proportions of late stage CVC.

Data describing county level population density (i.e. urbanicity) and the number of counties that were persistently poor for three decades in 2010 were extracted from the Economic Resource Services (ERS) agency.⁵⁷ According to the literature, late stage CVC diagnosis and access to CVC screening are significantly associated with both geography and socioeconomic status (SES).^{4,8} Studies suggest that women with lower income and in specific regions of the US are more likely to be diagnosed at a late stage.^{4,8} Further, a study by Aker et al. reported that women in rural areas and those in economically deprived non-rural communities are less likely to screen for CVC and report lower screening rates compared to women in urban and suburban areas.⁵⁵ Another 2014 survey study investigating rural populations and CVC screening also found that 71% of rural Appalachian respondents reported “not being able to use public transportation to get to medical appointment” as a barrier to screening.⁵⁸ Therefore, we include these county area contextual variables in our model to determine whether places that are less urban and places that are persistently poor are associated with higher proportions of later stage CVC.

The Health Professional Shortage Area (HPSA) score variable, which represents the score for determining priorities for assignment of clinicians within Primary Care Physician (PCP) shortage areas was obtained from the Health Resources and Service Administration (HRSA) database.⁵⁹ Scores range from 1-26, with higher scores reflecting greater priority and greater need. The number of Federally Qualified Health Centers (FQHC), Planned Parenthood (PPH) clinics and Title X-funded centers was obtained from Guttmacher Institute’s Contraceptive Needs and Services 2013 data report. We recoded each of the three health center count variables into rates per 100,000 people by multiplying each of the counts by 100,000 and dividing the product by the total US population for each county in 2010. The relationships between either high priority PCP shortage areas, or availability of federally funded health centers per 100,000 people with proportions of late stage CVC have never been explored. It is our hypothesis that these variables represent essential access to care barriers that will significantly impact the pathways to screening utilization and from screening to stage at CVC diagnosis. Specifically, we expect that the HPSA score represents lack of availability of CVC screening services, a known dimension of access to care. Similarly, the per-capita number of federally funded health centers represents both availability of services and affordability of CVC services, as these centers were developed with the specific goal of providing high quality and comprehensive primary care to medically underserved populations, regardless of their ability to pay.⁶⁰⁻⁶¹

State- Level Explanatory Variables

State- level variables were also extracted from a number of external data sources. Cervical cancer screening rates were extracted from the Behavioral Risk Factor Surveillance System (BRFSS).⁶² Research suggests that the most significant predictor of late stage CVC diagnosis is current screening, which is largely impacted by access to care.^{5, 17-19} Thus, we control for this variable using BRFSS data at the state level to help explain the relationship between access to CVC screening and stage at CVC diagnosis. The percent of the state population insured by employers in private self-insured health plans in 2010 was obtained from the Agency for Healthcare Research and Quality (AHRQ).⁴³ Individuals in private self-insured plans a population that accounts more than 50% of employees - were exempt from state mandates and many of the ACA provisions.⁴¹ These exclusions potentially undermine the potential for ACA and state mandates to have their intended effects. Although never before examined, we hypothesize that these loopholes significantly influence the number of women with access to CVC screening and thus are associated with later stage at diagnosis.

Data describing state nurse practitioner regulations in 2012 and state cervical cancer screening mandates were extracted from the National Conference of State Legislatures.⁶³ We categorized states into two groups: those that allowed NP autonomy to practice independently and/or prescribe medication as “autonomy” and states that did not allow NP autonomy to practice independently as “no autonomy.” From that, we created a binary indicator variable for each state specifying whether or not they allowed NPs autonomy to diagnose, treat, and prescribe without physician oversight. The influence of policy level variables on stage at CVC diagnosis is underexplored in the current literature. As described above, it is our hypothesis that the heterogeneity in these variables across states plays a huge role in access to CVC screening and pathways to late stage CVC diagnosis.

Statistical Analysis

Descriptive statistics for the outcome and predictor variables were computed using SAS statistical software and are included in Table 1. Two descriptive maps were also created to visualize the extent of the variation in proportion of late stage CVC diagnoses across counties and states (Figure of Maps 1-2). Mapping was done in QGIS software using standard deviation features that group rates by how many standard deviations (<2 sd : >2 sd) they are from the average county or national rate. This approach allowed us to visualize state- and county-level proportions of late stage CVC relative to the overall averages and provided evidence for the need to examine state and county predictors.

To examine predictors of higher proportions of late stage CVC, we estimated a multilevel model using data from county- and state -levels. With counties nested within states, we specifically used General Linear Mixed Model (GLMM) to fit a two-level random intercept model, which allowed state intercepts to vary. Several county- and state-level covariates and one state-level interaction between percent of the state population in self-insured plans and CVC screening mandates were included in the model. Final random and fixed parameter estimates were calculated using Full Maximum Likelihood (FML) estimation in SAS 9.2 statistical software. We selected this model framework because it has been found to be the most efficient model for assessing correlated data or predictors at various levels simultaneously. Also, failing to adjust for existing multilevel effects is equivalent to having omitted variables in the model, which can bias standard errors and p-values for the estimated regression parameters.⁴⁹ Ultimately, this model produces robust and reliable point estimates for study covariates. Together model estimation and mapping results helped to answer the following research questions:

- Controlling for other variables, are counties with fewer federally funded health centers per 100,000 people associated with higher county-level proportions of late stage CVC?
- Controlling for other variables, are counties with higher HPSA scores (greater need) associated with higher county-level proportions of late stage CVC?
- Controlling for other variables, are states with higher private self-insured rates associated with higher county-level proportions of late stage CVC?
- Controlling for other variables, are states with restrictive NP regulations associated with higher county- level proportions of late stage CVC?

- Controlling for other variables, are states without CVC screening mandates associated with higher county-level proportions of late stage CVC?
- Does the effect of CVC screening mandates on the proportions of late stage CVC depend on state-level private self-insured rates?

Results

Descriptive Statistics

During 2010-2014, the county-level average number of CVC cases among 2,357 counties is 25. Among these counties, the average percent of White women with CVC is 75.9%, Black women is 11.9%, Hispanic women is 7.94%, American Indian women is 1.92%, Asian women is 1.35% and women of Other race or ethnicity is 1% . The sample also indicates that the average county-level percent of women with CVC that were less than age 50 was approximately 48%. The CVC sample also shows that at the county-level an average of 55.56% of all CVC cases diagnosed during this period were late stage diagnoses. However, **Figures 1-2** show that the proportion of late stage CVC varies tremendously across counties and states. In regards to county-level variation, we found that in 379 counties the proportion of CVC cases diagnosed at a late stage was 1 standard deviation above the county- level average of 56% while the proportion of CVC cases diagnosed at a late stage CVC was 1 standard deviation below the county- level average in 187 counties. Given the substantial variability in the proportion of CVC cases diagnosed at late stage across counties and states, it is our hypothesis that both county- and state- level factors contributed to late stage CVC incidence and geographic disparities. **Table 1** provides the sample statistics for each of the county- and state- level study predictors.

On average, the county-level percent of individuals that speak English poorly was approximately 2%. We also found that there were more FQHCs than PPH clinics per capita, with approximately 2.07 FQHCs per 100,000 people and less than 1 PPH clinic per 100,000 people in the US. In regard to HPSA score, there was a county-level average score of 8.21. In regards to poverty, we found that approximately 13% of counties were persistently poor for the past three decades. Finally, we found that there was an average of 310 people per square mile across counties, indicating that counties were more rural than urban.

At the state-level, approximately 60% of states had a CVC screening mandate and approximately 56% of states did not allow NP autonomy to practice independently (i.e. no autonomy). We also found that the average percent of the state population insured by employers in private self-insured plans and underserved by primary care providers were 59.47% and 11.59% respectively. Finally, we found that the state-level average rate for Pap screening in 2012 was 77.38%.

Multilevel Model Results

In **Table 2**, we provide the empirical results from multilevel modeling of ecological factors at the county- and state- levels with state-level factors as higher levels of influence. The column in Table 2 labeled “base model” reports effect estimates when no interaction term is included in the model. Examining base model results, we found that both counties with higher proportions of women with CVC under age 50 and counties with more PPH clinics per 100,000 people exhibited lower proportions of late-stage CVC than counties with lower levels of these variables. Specifically, model estimation shows that for every 1% increase in the county- level percent of women with CVC under age 50 there is a 0.26 of a percent decrease in the percent of late stage CVC across counties, controlling for all study predictors. At the county- level we also found that a 1 clinic increase in PPH clinics per 100,000 people is associated with a 0.02 point decrease in the proportion of late stage CVC across counties, controlling for all study predictors. On the other hand, the average county-level HPSA score was the only significant predictor positively associated with the proportion of late stage CVC across counties in the base model. At the county level, for every 1 point increase in the HPSA score there is a 0.002 point increase in the proportion of late stage CVC across counties, controlling for all study predictors.

In the base model, no other county-level variables were found to be significantly associated with the average proportion of late stage CVC across counties. Although states varied widely in their regulations for NPs, CVC screening mandates and percent of the state population in self-insured plans, the base model also indicates that when controlling for all other study predictors none of these state- level variables are significantly associated with the average proportion of late stage CVC across counties.

Table 2 also reports the effect estimates when the state-level interaction between CVC screening mandates and percent of the state population in self-insured plans are included. These estimates are under the column labeled “interaction.” In this model, we found that age less than 50, PPH

clinics per 100,000 people and HPSA score were still statistically significantly associated with the proportion of late stage CVC across counties. The interaction model estimates also tell us that the two policy variables (CVC screening mandates and percent of the state population in self-insured plans) were statistically significantly associated with the county-level proportion of late stage CVC. Finally, we found that there was a statistically significant interaction effect between CVC screening mandates and percent of the state population in self-insured plans. Understanding these effect estimates requires computing the marginal effects, which involves both terms – the main effects and the interaction effect.

Model estimation suggests that the effect of the percent of the state population in self-insured plans on the county-level proportion of late stage diagnosis differs by whether or not the state has CVC screening mandates. Specifically, the marginal effects of the percent of the state population in self-insured plans on the proportions of late-stage CVC diagnosis in states with and without CVC screening mandates are as follows:

$$dY/dXSELF = 0.00523 +(- 0.00469) \text{ (when mandate=1)} = 0.00054$$

$$dY/dXSELF = 0.00523 +(- 0.00469) \text{ (when mandate=0)} = 0.00523$$

These results imply that a positive relationship between the percent of the state population in self-insured plans and the proportions of late-stage diagnosis existed in states with and without CVC screening mandates. However, this positive association was statistically significantly reduced in those states that had state CVC screening mandates. Specifically, higher proportions of the state population in self-insured plans were associated with lower county- level proportions of late-stage diagnosis in states with CVC mandates compared to states without CVC screening mandates.

Goodness of fit statistics (AIC) suggest that both the base and interaction models have better model fits compared to the null model. However, AIC statistics indicate that the base model has a better model fit compared to the interaction model, 210 and 216.3 respectively. Although the interaction model has a larger AIC compared to the base model, there is a strong theoretical underpinning and evidence in the existing literature that suggests that there is a significant interaction between CVC screening mandates and self-insured rates. Thus, we believed the

interaction model was still a reasonable model to estimate and the results of this model are reliable. (**Table 2**)

Discussion

At the county-level we found that more than 55% of all CVC cases were diagnosed at a late stage during the time period 2010-2014. Study results also indicate that there is extreme variability in the proportion of late stage CVC across counties and states (**Figures 1-2**). This suggests that there are significant geographic disparities in late-stage CVC and that both factors at the county- and state- level may contribute to these disparities. Based on limitations in the existing literature, it was our hypothesis that these factors were mostly unexplored access to care barriers that varied across both geographic and socioecological levels. This study adds to the current body of literature by being the first to investigate and report findings on the multilevel access barriers influencing county-level proportions of late stage CVC and geographic disparities. This study is also the first to focus specifically on the relationship between late stage CVC and several state policies including: NP regulations, CVC screening mandates and the proportion of the state population in private self-insured plans.

Among compositional factors, age less than 50 was the only factor statistically significantly associated with county-level proportion of late stage CVC. Specifically, counties with higher proportions of women with CVC under age 50 were associated with lower proportions of late-stage CVC. It is plausible that counties with higher proportions of women with CVC under age 50 were associated with lower proportions of late-stage CVC because women of childbearing ages (i.e. <50 years) are more likely to have regular contact with reproductive healthcare providers and thus provided with more opportunities to adhere to CVC screening guidelines compared to women over 50. This highlights the need to increase the number of CVC screening programs and interventions that target women over age 50. More specifically, future intervention strategies could focus on changing the way women over 50 interact with the healthcare system, encouraging more regular primary healthcare visits. These visits would provide women over 50 with more opportunities to adhere to CVC screening guidelines.

While there was only one compositional factor associated with county-level proportions of late stage CVC, there were a number of contextual factors statistically significantly associated with

late stage CVC. As expected, places with higher county- level HPSA scores (greater need) were statistically significantly associated with higher proportions of late stage CVC. The shortage of primary care physicians has been a well-known issue in the US for some time.⁶⁴ This shortage was worsened by an aging population and an increased demand for physicians due to millions being newly insured under expanded insurance coverage provisions of the ACA beginning in 2014.⁶⁵ An existing shortage of PCPs and a newly developed need for physicians, creates an environment where there is poor access to healthcare services, including CVC screening. Thus, it was no surprise that counties that are high priority PCP shortage areas exhibited higher proportions of late stage CVC. This suggests that there is a need to find effective solutions to the growing need for primary care providers and emphasizes how important these solutions are for increasing access to those healthcare services that prevents adverse health outcomes such as late stage CVC.

A number of solutions to the PCP shortage have been proposed, including expanding the role of NPs and having less restrictive NP regulations.^{31-32,66} Therefore, we expected that states with less restrictive NP regulations would have lower county-level proportions of late-stage CVC.

Although model results show that states with less restrictive NP regulations were in fact associated with lower county-level proportions of late-stage CVC, this relationship was not statistically significant (**Table 2**). While less restrictive NP regulations may be a viable strategy for improving access to healthcare services³³, it is plausible that the relationship between NP regulations and county-level proportions of late stage CVC depends on other factors not explored in the current study. For example, having less restrictive NP regulations is most important in rural areas where few supervising physicians are in close proximity and readily available to provide authorization via signatures. Thus, it is possible that a statistically significant relationship between NP regulations and county-level proportions of late stage CVC can only be observed when considering the interaction between NP regulations and urbanicity. Although our study controls for several factors including urbanicity, additional research is needed to determine what interactive and confounding effects impact the relationship between NP regulations and county-level proportions of late stage CVC.

In addition to the PCP shortage being an access to care barrier influencing late stage CVC diagnosis, our results also suggest that fewer PPH clinics per 100,000 people was another access

barrier influencing stage at CVC diagnosis. Planned Parenthood clinics are publicly funded institutes that provide free or low cost reproductive and preventive services, including CVC screening, to individuals that are predominately racial and ethnic minority and low income.⁶⁷⁻⁶⁹ Given their service population, these results suggest that places with fewer PPH clinics per 100,000 people are associated with geographical disparities in late stage CVC and plausibly socio-economic and racial disparities in stage at diagnosis. These results are of extreme relevance, as Planned Parenthood announced that they would voluntarily withdraw from Title X federal family funding programs, which provides PPH with nearly \$60 million annually, rather than comply with new laws that forbids referrals to doctors who can perform abortions.⁷⁰ Based on our results, it is our hypothesis that a significant lost in funding would restrict access to PPH clinics CVC screening services and thus impose a greater burden of late stage CVC in specific geographic areas.

Overall our base model results suggest a number of county- level access barriers associated with higher proportions of late stage CVC, however, our interaction model results suggest that state-level policies also play a role in stage at CVC diagnosis. Specifically, we found that the two policy variables (CVC screening mandates and percent of the state population in self-insured plans) were statistically significantly associated with the county-level proportion of late stage CVC. We also found that there was a statistically significant interaction effect between CVC screening mandates and the percent of the state population in self-insured plans, indicating that the effect of one varies based on the level of the other. Neither of the two policy variables (CVC screening mandates and the percent of the state population in self-insured plans) were statistically significantly associated with late stage CVC in the base model. Therefore, interaction model results suggest that the associations between proportions of late stage CVC diagnosis and these two policies could not be discovered without controlling statistically for the effects of their interaction. This highlights the importance of considering these variables together when the aim is to determine their relationship with outcome variables, as our study shows that this approach can reduce confounding.

When considering the interaction between CVC screening mandates and the percent of the state population in self-insured plans, the observed findings were as expected. We found that states with higher proportions of the state population in self-insured plans were associated with higher

proportions of late stage CVC and this disparity was most pronounced when there was not a state CVC screening mandate. Although private self -insured plans are exempt from state mandates, state CVC screening mandates' ability to lower the positive association between the percent of the state population in self-insured plans and proportions of late stage CVC could plausibly be explained by two underlying associations. First, it is plausible that some self -insured plans voluntarily covered CVC screening to avoid employee complaints. Second, it is also possible that some private self- insured employers in states with greater need of CVC screening (higher late-stage CVC rates) voluntarily covered CVC screening irrespective of being mandated to do so by state government, because it made good economic sense. Similar results were found in a 2019 study examining the extent to which health plan expenditures for infertility services differed by whether coverage was provided by self-insured plan versus fully insured plans and by whether patients resided in states with or without mandates requiring coverage for infertility services.⁷¹ They found that there were higher infertility treatment expenditures for self-insured employers in states with mandates compared to states without mandates.⁷¹

In conclusion, study results suggest that there are significant geographic disparities in the late stage CVC diagnoses and that both factors at the county- and state- level contribute to these disparities. Specifically, there are significant county- and state- level access to care barriers influencing stage at CVC diagnosis. These barriers include primary care physician shortages, a lack of Planned Parenthood clinics and the absence of CVC screening mandates in states with higher proportions of the state population in self-insured plans. Addressing these barriers by way of policy change or targeted CVC interventions is essential to reducing the burden of late stage CVC in specific geographic areas. Based on our findings we recommend that cancer control interventions target counties with fewer PPH clinics per 100,000 people and counties with higher HPSA scores and proportions of women with CVC who are over the age of 50. Without doing such CVC mortality rates will remain high and at a disproportionately higher rate for women in some geographic areas.

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Figure 1

The Proportion of Late Stage Cervical Cancer Across States during 2010-2014
(Standard Deviation Map)

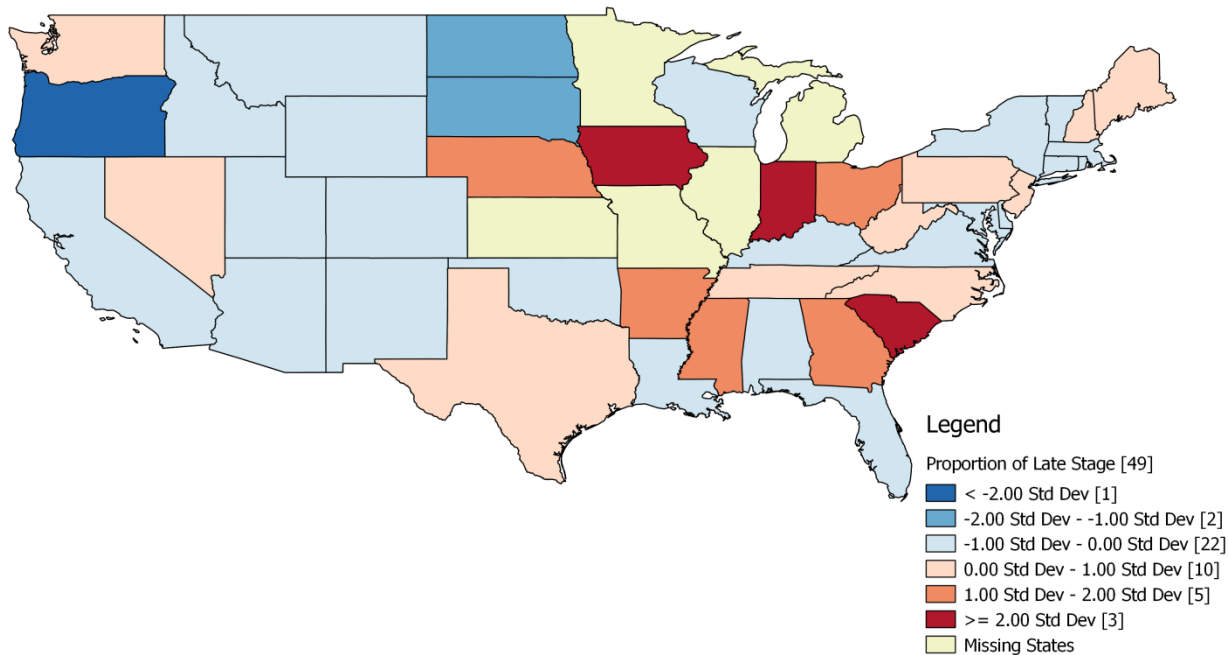


Figure 2

The Proportion of Late Stage Cervical Cancer Across Counties during 2010-2014
(Standard Deviation Map)

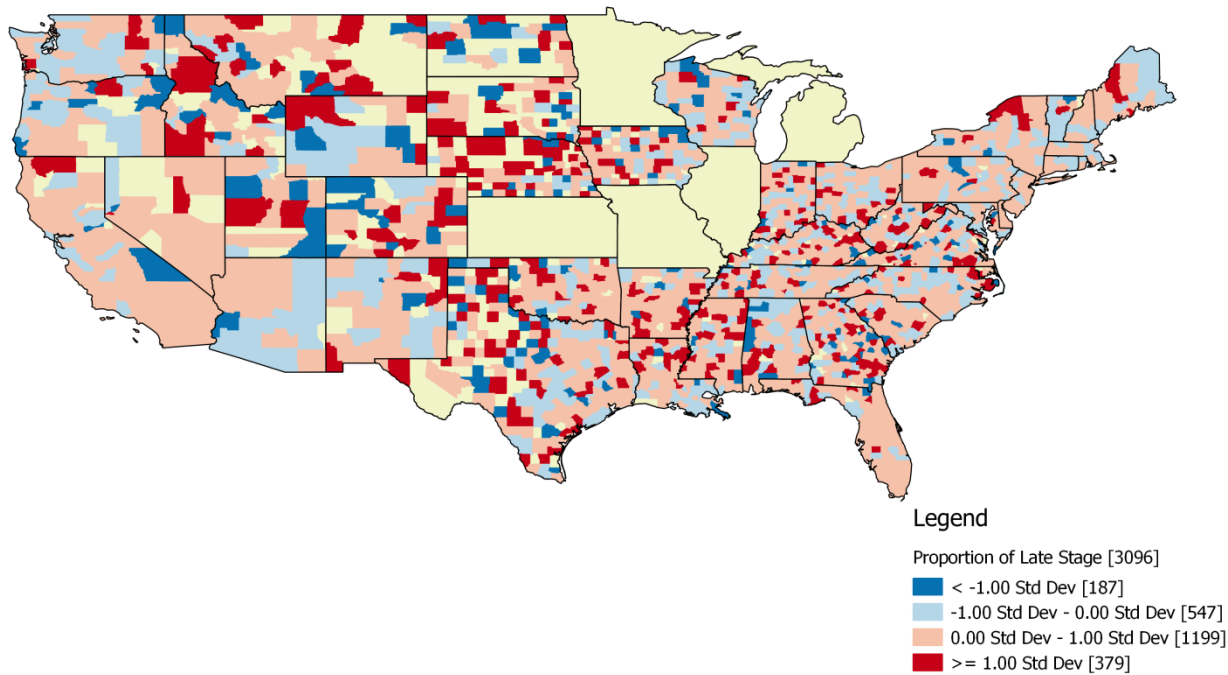


Table 1: Descriptive Statistics

County Data (n=2,357)			
Variable Name	Mean or proportion	Standard deviation	Minimum and maximum values
Late-stage CVC	0.5556	0.2564	0,1
Age < 50	0.4792	0.2472	0,1
American Indian	0.0192	0.0977	0,1
Asian	0.0135	0.0513	0,1
Non-Hispanic Black	0.1190	0.2170	0,1
Hispanic	0.0794	0.1749	0,1
Other	0.0094	0.0543	0,1
Non-Hispanic White	0.7593	0.2809	0,1
Proportion Speaking English poorly	0.0193	0.0607	0, 0.8286
Urbanicity =pop10/land	310.4118	1971.6079	0, 69178.9916
FQHCs per 100,000 people	2.0748	4.8789	0,100.35
PPH clinics per 100,000 people	0.2004	0.7267	0, 9.344
Title X funded clinics per 100,000 people	3.8968	5.4676	0,63.271
HPSA-score	8.2126	5.1585	0,24
Persistent Poverty			
No	2035 (87.11%)	NA, binary variable	NA, binary variable
Yes	301 (12.89%)		
State Data (n=43)			
Pap Screening rate in 2012	77.3813	3.1797	68.50,82.20
% of the state population in self-insured plans	59.4720	6.8522	46.70, 73.50
Underserved by a PCP	11.5977	6.9340	0.3252, 31.507
Nurse Practitioner Regulations in 2012			
No Autonomy	19 (44.19%)	NA, binary variable	NA, binary variable
Autonomy	24 (55.81%)		
CVC screening mandate			
No	17 (39.53%)	NA, binary variable	NA, binary variable
Yes	26 (60.47%)		

Table 2: Ecological Model Results

Covariate	Base Model Coefficient	Error	p-value	Interaction Coefficient	Error	p-value
County compositional variable						
Intercept	0.7696	0.2398	0.0027	0.5375	0.2564	0.043
American Indian	-0.05468	0.05785	0.3447	-0.0517	0.05761	0.3696
Asian	0.08512	0.1118	0.4465	0.07221	0.1118	0.5186
Non-Hispanic Black	0.02043	0.03013	0.4977	0.0189	0.02993	0.5278
Hispanic	0.02820	0.04187	0.5008	0.0246	0.04165	0.5549
Other	0.06428	0.1171	0.5830	0.06649	0.117	0.57
Non-Hispanic White	0	-	-	0	-	-
Age <50	-0.2637	0.02182	<.0001	-0.2635	0.02182	<.0001
County contextual Variable						
PPH clinics per 100,000 people	-0.02015	0.008489	0.0177	-0.01957	0.008454	0.0207
FQHCs per 100,000 people	0.000659	0.001146	0.5653	0.0007	0.001145	0.5411
TitleX funded clinics per 100,000 people	0.000357	0.001093	0.7438	0.000442	0.00109	0.6853
HPSA Score	0.002255	0.001122	0.0446	0.002365	0.00112	0.0348
Proportion Speaking English poorly	0.05543	0.1157	0.6320	0.05575	0.1155	0.6293
Urbanicity=pop10/land	-1.49E-6	2.733E-6	0.5844	-1.63E-06	2.73E-06	0.5494
Persistent Poverty						
Yes	0.01853	0.01818	0.3083	0.019660	0.01813	0.2784
No (REF)	0		-	0		-
State contextual Variable						
CVC Screening rate in 2012	-0.00296	0.002836	0.2965	-0.00262	0.002677	0.3281
% of state population in Self Insured plans	0.002052	0.001201	0.0875	0.005238	0.001913	0.0062
Percent Underserved by a PCP %	-0.00024	0.001267	0.8469	0.000047	0.001206	0.9686
CVC screening						

mandate						
Yes	0.004500	0.01712	0.7927	0.2935	0.14	0.0361
No (REF)	0		-	0		
Nurse Practitioner Regulations in 2012						
Autonomy (REF)	-0.01866	0.01621	0.2498	-0.010940	0.01553	0.4811
No Autonomy	0		-	0		-
Xself13* State CVC Mandate	-	-	-	-0.00469	0.002259	0.0382
Variance Components (state level)	0.000934	0.000540	0.0419	0.00067	0.000502	0.091
Variance Components (county- level)	0.05981	0.001820	<.0001	0.05984	0.001823	<.0001
Goodness of fit *AIC of null 278	AIC=210			AIC=216.3		

Chapter 5

Summary of Background, Gaps in Literature and Specific Aims

Approximately 51% of women with cervical cancer (CVC) are diagnosed at a late stage (regional or distant),¹ an outcome associated with increased morbidity and mortality.² African American,³⁻⁴ Hispanic women,³ and women residing in specific geographic regions of the US are among those most heavily burdened by late stage CVC.³ Existing literature suggests that the most significant predictor of late stage CVC diagnosis and disparities is current screening (i.e. having a Pap smear within the past three years), which is largely impacted by access to care.⁵⁻⁷ Provisions under the ACA, including expanded insurance coverage options available to people with pre-existing conditions beginning in 2010, mandated coverage of CVC screening without cost-sharing beginning in 2012 and Medicaid expansion beginning in 2014, have helped to mitigate the issue of poor access to healthcare.⁸⁻¹⁰ However, limitations and loopholes that reduce the intended effects of the ACA suggest that access to care is still a significant contributor of late stage CVC and disparities.¹⁰⁻¹³ Thus, the overall goal of this three-part study was to identify access-related predictors of late stage CVC and develop a comprehensive understanding of *where* and *why* racial and geographic disparities in late stage CVC occur.

While several studies have helped to advance our understanding of disparities in stage at CVC diagnosis and their relationship with access to care, the majority of the studies in the literature are either outdated, included a small sample of the US population, or presented notable limitations in their modeling approaches. To address these limitations and to fill gaps in the literature, we applied unexplored model-based constructs, novel spatial and multilevel methodologies and examined 43 states in the USCS cancer registry database, to carry out three specific aims, as follows:

- **Aim 1:** Using spatial autocorrelation methods, we identified clusters of counties considered to be high risk for late stage CVC “hotspots” during two 5-year time periods (pre- and post-2010), determined whether hotspots were associated with various contextual and compositional factors and determined whether there were hotspots that persisted over both time periods.

- **Aim 2:** Using multilevel modeling methods, we examined the relationship between the odds of late stage CVC among women and various individual- and county - level predictors, with a primary focus on unexplored measures of the availability and affordability constructs of the Theory of Access described in Chapter 1. Under this aim we also determined whether the unexplored measures of the availability and affordability were associated with racial or ethnic disparities in late stage CVC. The primary predictive measures of interest were primary care physician shortage areas and the number of CHCs and other publicly funded clinics available per 100,000 people.
- **Aim 3:** Using ecological multilevel modeling methods, we examined county-level disparities in late stage CVC across 43 states in the United States and explained the observed geographic disparities with numerous covariates. We identified statistically significant ecological relationships between high proportions of late stage CVC diagnoses in counties and several county and state-level access to care predictors. Among the study predictors, we primarily focused on unexplored measures of the health policy construct outlined in the Access to Care Framework. The primary measures of interest included: state CVC screening mandates, percent of the population in self-insured plans and nurse practitioner regulations.

Summary of Results & Implications

Summary of Study 1 Results & Implications

Under study **Aim 1**, we not only found that the overall proportion of late stage CVC diagnoses increased from 47% to 54% over the two time periods, but that the distribution of late stage CVC across counties also changed over time. More specifically, we found that the distribution of “hotspot” clusters was different pre- and post- 2010 and that only a few hotspot clusters remained stationary over the two time periods. These results helped us to pinpoint geographical areas that were in greatest need of intervention during earlier times, more recent times and both time periods (i.e. worse places). Persistent late stage CVC hotspot clusters (i.e. worse places) were most apparent in California, Louisiana, Alabama and Georgia. Study Aim 1 results also helped us to determine whether the underlying factors associated with these hotspots changed over time. We found that demographic concentrations of Blacks were not associated with hotspot

clusters identified in the early period but were associated with hotspot clusters in the later period. Demographic concentrations of Hispanics were not associated with hotspot clusters identified during either time periods. We also found that the hotspot clusters identified in the later period were more strongly associated with access to care barriers than hotspot clusters identified in the earlier period. This suggests that over time access to care barriers likely became the primary drivers of late stage CVC diagnoses.

Ultimately, hotspot clusters showed that there was extreme variability in the proportion of late stage CVC across counties and that clusters often contained counties in adjacent states. These results confirm that there were geographical disparities in late stage CVC, as demonstrated on maps of the analytic results. Based on these results, we were also able to hypothesize that factors influencing late stage CVC likely exist at both the county and state level. By observing the change in the associations between hotspot clusters and various indicators of access to care over the two time periods, these results further helped us to generate reasonable hypotheses regarding which access to care barriers were and were not significantly mitigated by the ACA provisions implemented during 2010-2014. These results could inform future policies and research aiming to identify factors that potentially reduce the intended effects of the ACA. Furthermore, the associations between various access to care variables and the hotspot clusters identified in the later period helped us to generate hypotheses regarding what types of access to care barriers (i.e. structural, health market or policy) would be significant predictors of late stage CVC during 2010-2014 if they were included in a multivariate, predictive statistical model.

Summary of Study 2 Results & Implications

Given the considerable variability in the proportion of late stage CVC across counties observed in the results under Aim 1, we hypothesized that significant county level factors were likely associated with stage at diagnosis among women. Thus, under **study Aim 2**, we assessed the relationships with access to care barriers occurring at the county level while accounting for some consistently identified individual level factors associated with late stage CVC. To our knowledge, this study is unique. Consistent with previous literature, we found that Black and Hispanic women with CVC and women with CVC who were over the age of 50 exhibited greater odds of late-stage CVC compared to White women and women under age 50. This study's unique contribution was several significant findings at the county level. Results suggest that the

percent of the population that had moved into the county from a different *country* in the year prior and the number of Planned Parenthood (PPH) clinics per 100,000 people were both negatively associated with a woman's odds of late-stage CVC diagnosis. These findings suggest that as the value of these two county-level variables increased, the odds of late stage CVC among women with CVC decreased, on average. On the other hand, county-level percent of uninsured individuals and the percent of individuals in poverty were positively associated with a woman's odds of late stage CVC diagnosis. Finally, we found that the relationship between the number of Planned Parenthood clinics per 100,000 people and stage at cervical cancer diagnosis differ by a woman's race or ethnicity. Specifically, we found that a greater number of PPH clinics per 100,000 people was associated with lower odds of late stage diagnosis among Hispanic women with CVC as compared to White women with CVC.

The results from study Aim 2 ultimately highlight significant disparities in late stage CVC among racial or ethnic groups, the need to consider the influence of characteristics of place on individual health outcomes, and how important affordability of health care services is to health in the US. While the relationship between measures of availability of health care services and stage at diagnosis were insignificant, we found that several measures of affordability of health care were significantly associated with the odds of late stage CVC. Percent uninsured, percent in poverty and the number of PPH clinics (which provide services at low or no cost) all represent affordability of health care services and their relationship with stage at diagnosis among women suggests that future interventions should address cost and/or affordable coverage. Given that more PPH clinics is a protective factor for Hispanic women with CVC, future interventions should also focus on maintaining or increasing the number of publicly funded clinics to mitigate racial or ethnic disparities in health outcomes.

Summary of Study 3 Results & Implications

While we were interested in understanding what factors were associated with late stage diagnosis among women, we were also interested in understanding what factors were associated with the variability in late stage CVC among places (i.e., counties in the 43 states). Research using ecological modeling to explain geographic disparities in late stage CVC is less commonly done in the literature to date. Yet, this research can be essential for pinpointing those factors that either introduce benefits or barriers in specific places. Thus, under **study Aim 3**, we focused on

ecological relationships to identify significant factors associated with geographic disparities in late stage CVC. We found that counties with greater needs for primary care physicians and larger proportions of older women with CVC were significantly associated with higher proportions of late stage CVC among counties. In regards to state policy levers, we found that state level nurse practitioner regulations were not significantly associated with the proportion of late stage CVC among counties. However, we did find that an unexplored and interactive relationship between CVC screening mandates and self-insured rates was significantly associated with the proportion of late stage CVC among counties. Specifically, we found that that states with higher proportions of the population in self-insured plans were associated with higher proportions of late stage CVC and this disparity was most pronounced when there was not a state CVC screening mandate.

Self-insured plans account for more than 50% of persons with employer-sponsored health insurance.¹⁴ However, private employer self-funded plans are exempt from most state insurance laws, including mandated benefits.¹⁵ Thus, when studying the effects of these mandates by states, it is essential to consider how much of the self-insured population is in public or private plans yet before our study this had never been done. Although we expected a different relationship than what was observed, our significant results suggest that health policy plays an important role in the etiological pathway to late stage CVC diagnosis and should be further studied. For example, additional research should be carried out to determine what policies or health system changes are needed to mitigate the impact of primary care shortage areas or the effects of self-insured plans on the proportion of late stage CVC.

Our results suggest that primary care physician (PCP) shortages are associated with high proportions of late stage CVC. Yet, whether or not NPs (which were introduced into the healthcare system, in part, as a solution to the PCP shortage) have autonomy to practice independently is not associated with county level proportions of late stage CVC. Thus, other policies or intersections of policies should be explored to determine effective approaches to eliminating the effects of PCP shortage areas on the county level proportion of late stage CVC. Ultimately, the results under study Aim 3 demonstrate how impactful county-level interventions and state-level policies can be to population health and suggest the need to focus on developing more multilevel interventions.

Limitations

Although significant results were yielded, our three-part study demonstrated several study limitations. The most apparent study limitation was the use of an incomplete sample of the US population (n=43 states). Because seven states were excluded from each of the three studies, we were not able to generalize our study results to the entire US population. Carrying out LISA cluster analyses using data that excludes seven states imposes further limitations on *Study 1* results as the clustering of counties into distinct cluster groups (i.e. hotspots or coolspots) is based on whether or not a county is surrounded by neighboring counties with similar rates. Therefore, it is likely that the distribution of clusters across the US, during both the early and late period, would be different if the counties of the remaining seven states were included and assessed relative their neighboring counties.

In addition to the exclusion of seven states, another study limitation was that we only included a short list of individual level predictors of late stage CVC. Although the literature indicates that marital status, education, income, insurance type and usual source of care are individual level predictors of late stage CVC, we did not have access to many of these variables and thus could not control for them in *Study 2* multilevel model. Failure to account for these variables could likely bias study estimates. Finally, because late stage CVC is impacted by factors at the individual, county and state levels, it is possible that our study results may be limited by our use of a two rather than three-level model. Although there are several challenges associated with estimating and interpreting three-level models, we acknowledge that it is important to account for the true hierarchal suture of the data to more accurately model reality and derive unbiased estimates.

Future Research

Although the current studies yield insightful results, there are still several aspects of the etiological pathway to late stage CVC and disparities that are not well understood. As previously mentioned, study results suggest that PCP shortage areas are associated with stage at CVC diagnosis, yet less restrictive NP regulations which could increase the availability of providers offering primary care services are not associated with stage at diagnosis. Thus, additional research is needed to determine whether the relationship between NP regulations and stage at

CVC is dependent upon unexplored and interactive relationships with factors such as urbanicity or whether other factors that address the issue of PCP shortage areas are more effective in reducing the odds of late stage CVC. For example, tuition reimbursement incentives for students willing to serve in PCP shortage areas are alternative approaches to the PCP shortage and thus could be more effective in reducing the odds of late stage CVC compared to less restrictive NP regulations. Ultimately, there is a need to understand how to address PCP shortage areas so that it does not continue to serve as a barrier to CVC screening.

Additional research is also needed to more thoroughly understand the relationship between health policy changes implemented as a result of the Affordable Care Act and late stage CVC diagnoses and disparities. The current study included data from 2010-2014, which were the most recently available data during the onset of our study. While several provisions of the ACA were implemented during this time period, there are often delays in the effects of health policies. Thus, the effects of access to care barriers are expected to diminish over time, and carrying out the same studies using more current data would likely provide additional insights regarding the effects of the ACA on access to CVC screening and stage at CVC diagnosis. Further, based on the significant role self-insured plans played in stage at CVC diagnosis during 2010-2014, additional research is also needed to determine whether or how the role of self-insured enrollment rates in states changes during a later time period. Self-insured plans are exempt from state mandates and regulations, but *not* exempt from federal laws, such as provisions under the ACA, except through grandfathered plans, not subject to the new provisions, for a limited time period. Thus, research is needed to determine whether, as the number of grandfathered plans dwindles, high numbers of self-insured rates continue to reduce the intended effects of the ACA on access to CVC screening and, thus, stage at diagnosis.

In addition to carrying out similar studies using more current data, research is needed to understand those factors associated with disproportionately higher rates of late stage CVC among Hispanic and African American women and women over the age of 50. Although study findings suggest that the availability of PPH clinics plays a role in stage at diagnosis among Hispanic women, PPH clinic availability does not explain 100% of the observed differences in late stage CVC rates among Hispanic and White women. However, these findings do suggest that other unexplored indicators of access to care could play a significant role in these disparities. Thus,

future research should focus on identifying those access to care barriers associated with racial and age-based disparities in late stage CVC.

Although additional research is needed to understand racial, ethnic and age disparities in stage at CVC diagnoses, health disparities overall have been found to vary from place to place and race or ethnic disparities and geographic disparities are often confounded.¹⁶⁻¹⁸ Specifically, confounding interactions between race and place have been found to bias national estimates such that they suggest that racial disparities exist when in actuality whole regions with higher concentrations of minorities have worse outcomes.¹⁹ Consequently, conclusions and implications drawn at the national level may not reflect what each individual state may be experiencing or most benefited by. Thus, future research should aim to disentangle the effects of place from socio-demographic determinants of health and determine in what states access to care barriers such as publicly funded health center density and PCP shortage is associated with racial or ethnic disparities in late stage CVC diagnosis. These results could be used to present state-level officials with information concerning whether or not racial disparities in late stage CVC exists in their states and to encourage state based action and interventions to reduce late stage CVC diagnosis rates and disparities.

Finally, given that these significant access barriers occurred at various ecological and geographical levels, we recommend that future research and intervention efforts begin to focus more on multilevel and/or spatial approaches. Prior to our studies, neither advanced spatial analytic methods nor multilevel modeling had been applied in studies aiming to identify geographic areas in greater need of intervention and factors underlying racial or geographical disparities in stage at CVC diagnosis. Yet, these advanced methods have proven useful for public health surveillance and understanding disease etiology and disparities among an array of other health outcomes.

The current study applied such innovative multilevel model methods to estimate both an individual and county level model as well as a county and state level model. However, much could be gained from examining the simultaneous effects of factors occurring at not only two levels but at three levels. For example, estimating a three level model that accounts for factors occurring at the individual, county and state level together would more accurately reflect reality and thus allow researchers to derive a more comprehensive understanding of those barriers

impacting stage at CVC diagnosis. Ultimately, using more innovative research methods and intervention strategies could allow researchers to better understand and combat the issue of late stage CVC in the US.

Take Home Message

Overall, the results from these studies demonstrate that there are significant demographic and geographic disparities in late stage CVC, and that access to CVC screening plays a significant role in the etiological pathway to late stage diagnoses and disparities. We found that primary care physician shortage areas, the number of Planned Parenthood clinics per 100,000 people, area-level poverty rates, area-level uninsured rates, percent of the population that moved from a different country, state CVC screening mandates and proportion of the state population in self-insured employer health plans were statistically significant predictors of access to care associated with late stage CVC diagnoses and geographic disparities. We also found that Planned Parenthood clinics play an important role in reducing the odds of late stage CVC among Hispanic women with CVC. However, additional research is needed to understand those factors associated with higher odds of late stage CVC among African American women. Given that these significant access barriers occurred at various ecological and geographical levels, we recommend that future research and intervention efforts begin to focus more on multilevel and/or spatial approaches. With 51% of cervical cancer cases diagnosed at a late stage¹ it is important to utilize more innovative methods for identifying the factors associated with late stage cervical cancer diagnosis and disparities. Without doing such CVC mortality rates will remain high and at a disproportionately higher rate for women in various geographical areas and among African American and Hispanic women.²⁰⁻²²

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