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Effect of Primary Care Physician Density on Late Stage Cervical Cancer Diagnosis

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by

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ABSTRACT

INTRODUCTION: Late-stage cervical cancer diagnosis is an important contributing factor to the cervical cancer mortality rate. Screening for cervical cancer is a vital tool in reducing the number of late-stage cases, preventing incident cases and reducing mortality. Access to care is often a significant barrier to receiving these services. Women who have no usual source of care report significantly lower percentages of Pap tests than women who have a usual source. South Carolina ranks 13th in the US in cervical cancer incidence and 7th in cervical cancer mortality. South Carolina also struggles with a primary care physician shortage, ranking 39th in primary care physician density. This study aimed (1) To determine the demographic and geographic differences between early and late stage cases as well as the distribution of primary care physicians in South Carolina (2) To assess the relationship between primary care physician density and the risk of late-stage cervical cancer diagnosis. METHODS: Multivariate logistic regression models were used to assess the association of primary care physician density to late stage cervical cancer diagnosis. Both the main outcome and exposure were mapped.

RESULTS: Out of 1,992 cervical cancer cases from 2000-2010 44.78% were diagnosed late-stage. Census tracts with greater than 0 primary care physicians per 100,000 persons had significantly lower odds of late-stage diagnosis than census tracts with 0 primary care physicians per 100,000 persons. African-American women, cases diagnosed after 2003, and older women all had significantly higher odds of late stage diagnosis.

CONCLUSION: Areas with low primary care physician density and high late stage diagnosis should be a focus of in cervical cancer screening interventions.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACS.. American Cancer Society

ACOG .... American College of Obstetricians and Gynecologists

AJCC.. American Joint Committee on Cancer

CDC .... Center for Disease Control and Prevention

HPSA .... Primary Care Health Professional Shortage Area

HRSA.. Health Resources and Services Administration

HPV.. Human Papillomavirus

IRB .... Institutional Review Board

IUD .... Intrauterine device

MUA .... Medically Underserved Area

NAACR.. North American Association of Cancer Registries

NHIS .... National Health Interview Survey

Pap.. Papanicolaou

PCP .... Primary Care Physician

SCCCR.. South Carolina Central Cancer Registry

SEER.. Surveillance, Epidemiology, and End Results

SES.. Socioeconomic status

USPSTF .... US Preventive Services Task Force

CHAPTER I.

INTRODUCTION

1.1 Statement of the problem

Cervical cancer was the most common female cancer in the United States 40 years ago.[1] Due to widespread use of the Papanicolaou (Pap) test, the incidence rate of cervical cancer dropped from 17.2 to 8.0 per 100,000 persons from 1973 to 1999. The mortality rate fell accordingly from 6.2 to 2.9 per 100,000.[2] However for 2014, there will be an estimated 12,360 incident cases of cervical cancer and an estimated 4,020 deaths.[3] The Healthy People 2020 initiative has set goals to reduce the mortality rate of cervical cancer by 10 percent from the baseline of 2.4 (per 100,000 persons) in 2007 to a target of 2.2 by 2020. It also aims to reduce the incident rate of invasive cervical cancer by 10 percent from 7.9 cases (per 100,000) to 7.1 cases.[4]

Human Papillomavirus (HPV) has been demonstrated to be a necessary cause of cervical cancer and HPV strains 16 and 18 make up approximately 70% of all cervical cancers.[5] The preinvasive lesions that result from persistent oncogenic HPV infections are typically asymptomatic and only discovered by a Pap test. If the lesions are left untreated, the lesions can extend from the surface cervical epithelium through the full thickness epithelium and eventually through the basement membrane to become invasive cervical cancer.[6]

The U.S. Preventive Services Task Force (USPSTF) recommends that women aged 21 to 65 get a Pap test once every three years.[7] Data from the 2010 National Health Interview Survey (NHIS) have shown that among women who have not had a hysterectomy, 83% had a Pap test within the past three years.[8] This percent is much lower among women who have no usual source of care. Only 64.9% of these women had a Pap test within the past three years. A similar percentage was reported for women who are uninsured (63.8%), making access to care an important barrier to cervical cancer screening.[9] In a case-control study, women who had not received a Pap test had a significant 2.7 relative risk increase of invasive cervical cancer as compared to women who had received a Pap test. Following the guidelines for Pap tests is key in the prevention of cervical cancer.

Cervical cancer is categorized into stages when it is diagnosed: localized, regional and distant. The American Joint Committee on Cancer (AJCC) also defines stages numerically. These stages 0-4 are based on the TMN system or the extent of the tumor, whether the tumor as spread to the lymph nodes and whether it has spread to other sites.[10] The AJCC stages align with localized, regional and distant categorization except AJCC includes *in situ* cases as stage 0. *In situ* cases refer to cases where the cancer cells are only located on the surface of the cervix and have not invaded any deeper cervical tissues.[10] Localized refers to an invasive malignant neoplasm confined entirely to the cervix with no lymph node involvement. Regional is a malignant neoplasm that has extended beyond the limits of the cervix directly into surrounding organs or tissues or it involves regional lymph nodes by way of the lymphatic system or it has both regional extension and the involvement of regional lymph nodes. A distant classification requires a malignant neoplasm that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.[11] The distribution of stage diagnosis for cervical cancer cases in the U.S. from 2003-2009 is as follows: 47% localized, 36% regional, 12% distant, and 4% unknown or unstaged.[11]

The absence of Pap tests is one of the most commonly attributed risk factors for invasive cervical cancer.[12] An established barrier for cervical cancer screening is access to care.[13] Lack of services or lack of physicians greatly hampers a woman's ability to receive proper screening, diagnosis, and treatment for cervical cancer as recommended.[13] Physicians are often unevenly distributed leading to disparities in rural and low-income areas.[14]

The United States is currently experiencing primary care physician shortage problems. The Health Resources and Services Administration (HRSA) recognizes 5,900 areas as Primary Care Health Professional Shortage Areas (HPSA). This designation is for populations that have one (or less) primary care physician per 3,500 people.[15] This translates to approximately 29 primary care physicians per 100,000 persons. The shortage is exacerbated by the unequal distribution of primary care physicians in the United States. While there are approximately 80 primary care physicians per 100,000 people in the US, the averages are much different when broken down into urban and rural settings. Urban areas have 84 primary care physicians per 100,000, whereas rural areas have only 68 primary care physicians per 100,000.[14] This leaves many people without readily available care and can be influential in determining whether or not receive preventive medicine like a Pap test.

1.2 Significance

Early detection of cervical cancer is crucial in the reduction of cervical cancer mortality. Late-stage diagnosis of cervical cancer (distant) has a five-year survival rate of approximately 12%. Regional stage diagnosis has a five-year survival rate around 57%.[16] Conversely, an early diagnosis of cervical cancer (localized) has a five-year survival rate of approximately 90%.[17] Also contributing to cervical cancer outcomes is socioeconomic status. Having a lower socioeconomic status (SES) is associated with higher rates of late-stage diagnosis for cervical cancer as well as lower survival. Low SES has such a powerful impact on cervical cancer mortality that even after late-stage diagnosis is controlled for in statistical analysis, those living in high SES census tracts have a 30% greater 5-year survival rate than those living in low SES census tracts.[18]

Cervical cancer's burden on the population is grossly disproportionate. Over sixty percent of the cases in the United States are in populations of underserved and under-screened women.[9] Living in a medically underserved area (MUA) is also a significant predictor of late-stage diagnosis.[19] As of October 2012, South Carolina has 189 areas listed as Primary Care HPSAs.[15] Not having adequate access to care puts these women at a significant health disadvantage.

South Carolina has some of the highest incidence and mortality rates for cervical cancer in the country at 8.0 incident cases and 2.3 deaths per 100,000.[20] It also is ranked 13th highest in the nation for percentage of its population living in rural areas.[21] Making sure the large rural population in South Carolina has adequate access to health care is an important step in reducing the incidence and mortality of cervical cancer for the state.

1.3 Specific Aims

Late-stage diagnosis of cervical cancer has such drastically different survival rates than an early diagnosis that it is imperative to understand the risk factors contributing to the different outcomes. The lack of availability of health care has been shown to have a negative impact on stage of diagnosis for cancer, including cervical, in other states.[22–24] There has not been any prior exploration of the association between primary care physician density and late-stage diagnosis in South Carolina for cervical cancer. This thesis aims to determine:

1. The demographic and geographic differences between early and late stage cervical cancer diagnosis and the distribution of primary care physicians in South Carolina.
2. If there is an association between primary care physician density and the risk of late-stage diagnosis for cervical cancer in South Carolina.

Hypothesis: Greater primary care physician density will be associated with lower odds of late-stage cervical cancer diagnosis, adjusting for SES and other known covariates.

Finding an association between primary care physician density and late stage cervical cancer diagnosis will have an impact on health care policy and cancer screening interventions. This research has broad reaching implications and finding an effect will influence how future funding is spent to help equalize access to care and how best to target those most at risk for late stage cervical cancer. Screening interventions are most effective when they are able to reach those who need them most. By identifying risk factors for late stage diagnosis, we will be able to apply screening programs more effectively.

CHAPTER II.

LITERATURE REVIEW

2.1 Cervical Cancer in South Carolina

South Carolina was ranked 14th in the United States for incident cases of cervical cancer with an age-adjusted rate of 8.0 per 100,000 and 7th for mortality with an age-adjusted rate of 2.8 per 100,000 people for 2010.[20] In 2009, there were an estimated 170 incident cases and 60 deaths of cervical cancer in South Carolina.[25] HPV is a necessary, but not sufficient, cause of cervical cancer.[5] Risk factors for cervical cancer include tobacco use, parity, oral contraceptive use, previous sexually transmitted infection, and socioeconomic status.[18,26–28]

Racial disparities in stage of diagnosis and survival of cervical cancer have been documented.[29,30] African-American women had an incidence rate of 11.5 per 100,000 people compared to 7.5 per 100,000 people for European-American women in South Carolina from 2002-2006. The mortality rate for African-American women was also higher than European Americans in South Carolina for this same period at 4.9 per 100,000 compared to 1.9 per 100,000.[25]

Several counties in South Carolina have extremely high incidence and mortality rates. Both Orangeburg and Kershaw counties have cervical cancer incidence rates greater than 12.0 cases per 100,000 and mortality rates greater than 3.0 deaths per 100,00

(Figure 1, Figure 2). Sumter, Darlington, Florence, and Greenwood counties also have similar mortality rates, with the highest in Darlington of 5.0 cervical cancer deaths per 100,000 persons.[31] This is 78.6% greater than South Carolina mortality rate and 117% greater than the United States mortality rate for cervical cancer.[32] Other counties with very high incidence rates for 2000-2009 were Jasper, Bamberg, Chesterfield, Marlboro, Dillon, and Chester counties. Jasper County had a cervical cancer incidence rate of 17.7 cases per 100,000 persons; this is 121% greater than the South Carolina incidence rate and 136% greater than the national incidence rate.[31,32]

2.2 Human Papillomavirus (HPV)

The transition from HPV to cervical cancer has four steps: HPV acquisition, acute HPV infection, persistent HPV infection leading to precancerous changes, and invasive cervical cancer. These precancerous changes are called cervical intraepithelial neoplasia (CIN).[33] As this is a slow process, screening for HPV and/or cervical lesions is a primary prevention tool for cervical cancer. The U.S. Preventive Services Task Force recommends that women from age 21 to 65 receive a Papanicolaou (Pap) test once every three years.[33] In 2010, 73.2% of women in the United States, who have not had a hysterectomy, reported having a Pap test in the last three years.[34] South Carolina had a slightly higher percentage that same year, with 83.0% of women reporting having had a Pap test in the last three years.[8]

While there are many different types of HPV, 70% of oncogenic infections are caused by strains 16 and 18.[35] In a cohort study on the University of South Carolina campus measuring HPV persistence, 31.7% of the baseline population tested positive for HPV and of these infections 58.4% were identified as high risk (HPV 16, 66, 51, 52, and

18). HPV 16 accounted for 17.6% of all infections seen at enrollment.[36] In Dahlström *et al*, the risk of HPV 16 seropositive women to develop invasive cervical cancer was more than twice as high as the risk for seronegative women (OR =2.4; 95% CI, 2.0–3.0).[28]

Making sure women are screened on a regular basis is important in reducing the number of incident cases of cervical cancer in the United States. It is estimated that over 50% of women who developed cervical cancer did not have a Pap test in the last three to five years.[33] Not having access to health care greatly reduces the percentage of women who receive a Pap test. Only 64.9% of women who had no usual source of care and 63.8% of uninsured women had a Pap test in the last three years.[7]

2.3 Outcome of Interest: Cervical Cancer Stage at Diagnosis

Cervical cancer is broken down into stages when it is diagnosed: localized, regional and distant. The American Joint Committee on Cancer (AJCC) also defines stages numerically. These stages 0-4 are based on the TMN system or the extent of the tumor, whether the tumor as spread to the lymph nodes and whether it has spread to other sites.[10] The AJCC stages align with localized, regional and distant categorization except AJCC includes *in situ* cases as stage 0. *In situ* cases refer to cases where the cancer cells are only located on the surface of the cervix and have not invaded any deeper cervical tissues.[10] Localized refers to an invasive malignant neoplasm confined entirely to the cervix with no lymph node involvement. Regional is a malignant neoplasm that has extended beyond the limits of the cervix directly into surrounding organs or tissues or it involves regional lymph nodes by way of the lymphatic system or it has both regional extension and the involvement of regional lymph nodes. A distant classification requires a malignant neoplasm that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.[11] The distribution of stage diagnosis for cervical cancer in the United States for 2003-2009 is as follows: 47% localized, 36% regional, 12% distant, and 4% unknown or unstaged.[11] In South Carolina, the distribution by stage for 2003-2009 was 46.5% localized, 34.7% regional, 9.4% distant, and 9.4% unknown.[31]

Diagnosing cervical cancer early is central in reducing cervical cancer mortality. Late-stage diagnosis of cervical cancer (distant) has a five-year survival rate of approximately 12%. Conversely, an early diagnosis of cervical cancer (localized) has a five-year survival rate of approximately 90%.[17] The overall survival rate for cervical cancer from 2004-2010 was 67.9%.[16] While the survival and incidence rate has decreased significantly over the past 30 years, the percentage of women diagnosed with invasive cervical cancer at the localized stage has not changed much, 63% compared to 52% for 1975 and 2008, respectively.[37] This lack of change indicates that while the many cervical cancers are diagnosed at an early stage, there is a substantial proportion that progress to regional and distant stages prior to diagnosis.[37]In a national survey from 2004-2006, the Center for Disease Control and Prevention (CDC) found 47% of invasive cervical cancers were diagnosed late-stage.[38] This percentage varied by race/ethnicity with African Americans having the largest percentage of late-stage cases (52.8%) and Hispanic women with the lowest percentage (45.9%). Hispanic women also had the highest rate of early stage diagnosis at 7.5 cases per 100,000 persons. African American women and European

American women had relatively similar rates of early stage diagnosis at 5.5 and 5.3 cases per 100,000 persons respectively.[38]

2.4 Primary Exposure: Primary Care Physician Density Introduction

Primary care physicians play a significant role in a community's health. An increase of one primary care physician per 10,000 population has been associated with an average all-cause mortality reduction of 5.3 percent or 49 deaths per 100,000 per year.[39] Unfortunately, the United States has a primary care physician shortage problem. The Health Resources and Services Administration (HRSA) have designated 5,900 areas across the U.S. as Primary Care HPSAs. This designation is for populations that have one (or fewer) primary care physician per 3,500 people, which translates to 29 primary care physicians per 100,000 persons.[15] The United States also has thousands of Medically Underserved Areas (MUAs). Qualification as a MUA requires a service area score 62.0 or less out of 100 on the Index of Medical Underservice (IMU) where 0 is the completely underserved and 100 is the best served. The IMU takes into account the weighted ratio of primary medical care physicians per 1,000 population, infant mortality rate, percentage of the population with incomes below the poverty level, and the percentage of the population age 65 or over.[15]

2.5 Primary Care Physicians in South Carolina

In 2009, the physician-to-population ratio for South Carolina was 382 individuals per one physician. This ratio has been steadily increasing from 702 individuals per one physician in 1980. The increase seen in South Carolina is reflected in the United States' at large physician-to-population ratio, which increased from 513 individuals per one physician in 1980 to 320 individuals per one physician in 2009.[40] While South Carolina has been progressively improving on its physician-to-population ratio, the state still holds a large number of MUAs.[15] South Carolina currently has 46 counties reporting 189 Primary Care HPSAs and 44 counties reporting 270 Medically Underserved Areas[15]. In 2010, South Carolina had a total physician density of 215.8 per 100,000, ranking it 37th in the country. The national average physician density was 258.7 per 100,000. For primary care physician density, South Carolina ranked even lower at 39th with 77.4 primary care physicians per 100,000. The state with the highest primary care physician density was Massachusetts with 129.2 per 100,000.[41] In comparison, the United States primary care physician density was 90.6 per 100,000 in 2010.[42]

2.6 Primary Care Physicians and Cancer

The impact primary care physicians have on cancer can be substantial. In a study examining the role of primary care physician in cancer, it was found that over 75% of physicians surveyed fulfilled at least one of the key cancer care roles. The most common role included assessing patient treatment options and whether or not surgery was an option.[43] Making sure patients are well informed and comfortable with their treatment plan has led to lower anxiety and greater cancer patient satisfaction.[44] Primary care physicians also provide screening tests for and educational information about developing cancer. One survey found that 49% of women had a Pap smear performed by their primary care physician.[45] Women who lived in an area with less than 100 office-based primary care physicians per 100,000 women were statistically significantly less likely to report having had a Pap test in the past three years (83.5%) as compared to women who lived in an area with 500 or more office-based primary care physicians per 100,000 women (87.7%).[46] At a county-level, it has been found that an increase of one family physician per 10,000 persons was associated with a decrease in incidence of 1.5 cases per 100,000 and a decrease in mortality of 0.65 cases per 100,000 for cervical cancer.[23] Living in a MUA has also been found to be a significant predictor of late-stage cervical cancer diagnosis.[17]

Primary care physician density has been shown to have an effect on other cancers. An increase in the supply of primary care physicians has also been linked to early detection for breast cancer. Each tenth percentile increase in the primary care physician supply was associated with a 4% increase in the odds of early detection.[24] A study conducted in Illinois found that poor geographic access to primary care physicians was strongly associated with late-stage diagnosis for breast cancer. This finding is made even more interesting by the fact that there was no association found for spatial access to mammography and late-stage risk suggesting that primary care physicians may play a more significant role in preventing late-stage diagnosis.[47] Physicians also have an effect on cancer survival. An ecological study of women aged 40 years or greater in Florida found that as physician density decreased, the survival among women with breast cancer did as well.[48]

In low physician density populations, a 14% decrease in incident late-stage colorectal cancer was found for counties with higher primary care physician density. This negative association was found only in non-metropolitan areas, leading the study to advise that efforts aimed at increasing physician supply should target low-density underserved populations.[22] Other urologic cancers, specifically kidney and renal pelvis cancers, have demonstrated a negative relationship between mortality and physician density. Cancer mortality increased significantly as physician density decreased for the population. This study found a similar relationship for prostate and bladder cancers, although it was only suggestive and not statistically significant.[49] Primary care physicians can have a significant effect on cancer incidence, mortality, and stage of diagnosis. Targeting areas that are designated MUAs or HPSAs is an important step in reducing the cervical cancer burden in the United States.

2.5.1 Obstetricians and Gynecologists (OB/GYN) and Cervical Cancer

OB/GYNs are a frequent source for cervical cancer screening.[50–53] In a cross-sectional study of Texas primary care providers, which included OB/GYNs, 85.6% of OB/GYNs surveyed performed more than 25 Pap tests per week. The majority of family practice specialists (52.2%) and community internal medicine specialists (71.4%) performed Pap tests less than 10 times per week.[53] Seeing an OB/GYN has been found to be a strong predictor of receiving more screening and vaccinations.[54,52] One study predicting whether women aged 55 or older in Appalachia had recently received a Pap test found a highly significant odds ratio of 8.45 for women who saw an OB/GYN within the past year.[52] Women who visit either a gynecologist only, or a general physician and a gynecologist, are significantly more likely to receive a Pap test than women who visit a general physician only.[51] Having access to an OB/GYN has shown an effect on whether women reported having a Pap test within the past 3 years. Women who live in an area with less than 10 office-based OB/GYNs per 100,000 women had a statistically significant lower percentage reporting a Pap test performed within the past 3 years

(85.6%) as compared as to women who live in an area with 30 or more office-based OB/GYNs per 100,000 women (87.5%).[46]

2.6 Other Risk Factors

2.6.1 Race

Cervical cancer does not affect all races equally in terms of incidence and mortality. In South Carolina, a significant decrease in survival of African American woman was found as compared to European American women, even after adjusting for disease stage.[55] A Florida cohort study found African American women had significantly more regional and distance cancer diagnosis and more poorly differentiated tumors compared to European American women. The study also found that Hispanic women typically were diagnosed with a more advanced stage disease, but had a longer survival times.[56] This coincides with previous literature that has found 26-30% increased survival for Hispanic women compared to non-Hispanic women.[57,58] Interestingly, African American women have the highest rates of being screened for cervical cancer.[30] In South Carolina, 90.4% of African American woman and 84.5% of European American women had a Pap test within the past three years according to the 2008 Behavioral Risk Factor Surveillance Survey (BRFSS).[25]

There are several racial and ethnic differences for cervical cancer incidence rates. The CDC released a report examining HPV-associated cervical cancer age-adjusted rates for 2004-2008. It found incidence rates of 7.4 cases per 100,000 for Whites, 9.9 incident cases per 100,000 for Blacks, 6.5 incident cases per 100,000 for American Indian/Alaska Natives, and 7.1 incident cases per 100,000 for Asian/Pacific Islanders. Hispanics had an incident rate of 11.3 per 100,000 compared to a 7.4 per 100,000 incident case rate for

Non-Hispanics.[59] There are also racial-age disparities that continue to persist for older African American women (aged > 50 years).[60] African American women also have significant differences in treatment. After controlling for stage of disease, African American women are more likely to receive no treatment or radiation alone compared to surgery or combination of therapies than European Americans or Hispanics.[30] This may contribute to the high rate of mortality for African American women. Asian or Pacific Islander women have 68% greater cervical cancer prevalence currently than they have in past years. Asian and Pacific Islander is one of the fastest growing minority groups in the United States, which contributes to this increase in cases.[61]

2.6.2 Socioeconomic Status

Late-stage diagnosis of cervical cancer has been associated with low-socioeconomic status (SES).[62] Women who live in lower SES census tracts have significantly higher rates of cervical cancer incidence and mortality. After controlling for stage of disease, women who live in a low SES tract have a 30% lower 5-year survival rate than women who live in a high SES tract.[18]

In a Florida study with 5,367 women with cervical cancer, patients who lived in communities in which less than 15% of the population lived in poverty had significantly worse survival outcomes compared with communities in which there was less poverty.[56] Almost 60% of the African American patients in Brookfield *et al.* lived below 15% poverty, compared to 27.6% of European Americans. At every poverty level in the study African American women had a shorter median survival time[56] Decreased education levels has generally led to an increase in cervical cancer mortality for women of all racial and ethnic groups.[18] Having a low SES is such a key predictor of high cervical cancer incidence and mortality because of the barriers of access to care that a low SES presents. This is demonstrated most effectively in a military healthcare environment where everyone has as equal access to care. In a review of 1,553 cases of cervical cancer, no statistical difference between stage, incidence, mortality, and grade were found at diagnosis even after considering the variable races and SES statuses.[63]

2.6.3 Tobacco

Cigarettes contain known carcinogens and women who smoke cigarettes have a significantly greater risk of cervical cancer than nonsmokers (RR=3.42, 95% CI, 2.10 to 5.57). Exposure to second hand smoke has also been evaluated and found to have a risk estimate of 2.96 (95% CI, 1.23 to 7.03) for at least 3 hours of exposure per day.[27] Tobacco by-products have been found in the cervical mucus of women who smoke and are believed to damage the DNA of cervical cells promoting the development of cancer.[64]

European American women who had been diagnosed with cervical cancer were significantly more likely to have used tobacco than African American women. Among smokers, European American women had significantly longer survival than African American women, 47.7 months compared to 29.1 months.[56]

2.6.4 Insurance

Insurance can play an important role in access to care and whether or not a woman receives cervical cancer screening or treatment. Women, who are uninsured, have Medicaid, or Medicare have significantly higher risk of late-stage diagnosis of cervical cancer than women who are privately insured.[65] O'Malley *et al.* found that late-stage diagnosis was 2.8 times higher in women who were uninsured than women who were enrolled in Medicaid. Also, women who were only intermittently enrolled in Medicaid had 1.3 times lower late-stage diagnosis than those uninsured.[66] Another study examining Medicaid enrollment found that Medicaid insured approximately one-fourth of the women with cervical cancer. Women enrolled in Medicaid after they were diagnosed with cervical cancer were most likely to have a late-stage diagnosis as compared to women who insured before diagnosis. A statistically increased risk of death was associated with women younger than 65 and not enrolled in Medicaid (OR=2.4 95%CI, 1.49,3.86), which was surprisingly higher than the risk of death for women greater than 65 and not enrolled in Medicaid (OR=1.24 95% CI, 0.48, 3.19).[67]

2.6.5 Sexual and Reproductive Risk Factors

The age of first intercourse and number of sexual partners have been found to be independent risk factors for cervical cancer.[26,68] Previous exposure to chlamydia has been associated with a strong increased risk for cervical cancer.[26,28] It has suggested that the effect of a chlamydia infection occurs early in the carcinogenic process. Chlamydia may enable HPV persistence. Dahlström *et al.* found that chlamydia associated with seronegative HPV 16, implying chlamydia may increase the risk to contract HPV 16, or enable HPV 16 infections to persist.[69] The use of oral contraceptives is significantly associated with invasive cervical cancer if the contraceptives are used long enough. Oral contraceptive use up to four years have not shown any relationship, but use for longer than five years has been associated with a fourfold increase in the risk of invasive cervical cancer (95% CI, 2.1 to 5.5).[26]

A high parity has been linked to an increased risk of cervical cancer. In a Costa Rican study, women with four births had a 3.5 times increased risk compared to women who had one or no births. The study found a significant linear relationship for each sequential birth.[70] Intrauterine device (IUD) use has been found to have a strong and consistent inverse relationship with cervical cancer. Women who have previous IUD had half the risk of developing cervical cancer in Castellsagué *et al.* than women who did not have a history of IUD use.[71] The study hypothesized that the insertion or removal of an IUD produces a long lasting immune response or when the device is inserted or removed preinvasive cancer lesions are removed. An IUD was not found to prevent HPV, but it could alter the progression of HPV to cervical cancer and therefore could be considered a protective factor.[71]

2.6.6 Age

As cervical cancer is a slow-growing, it is more likely found in older women.[72] A retrospective study conducted with 1800 patients diagnosed with cervical cancer found that the disease is rare for women aged 20-24. There were more women diagnosed at age 26 (n=257) than the entire age group 20-24 (n=223). However, women who were diagnosed between age 20-24 were more likely to have a more advanced cancer and therefore, more aggressive treatment.[73] Age has been previously associated with an increased risk of late-stage diagnosis for cervical cancer.[74] Younger women are also more likely to receive a Pap smear test on a regular basis as compared to older women. A significantly higher rate of women not up-to-date on their cervical cancer screening (32%) was found among women aged 50 to 69 years compared to women aged 30 to 49 not up-to-date (20.3%) on their screening.[75]

2.6.7 Urban/Rural Geography

Long-term trends between rural and urban areas for cervical cancer persist today. From 1969-2007, while the overall mortality rate fell, rural non-metropolitan areas had a morality rate that was still significantly higher than urban metropolitan areas.[37] This difference between rural and urban rates held true for cervical cancer incidence as well. Rural women had an incidence rate 15% significantly greater than urban women. The rate of late-stage diagnosis for urban and rural women while different did not yield any statistical significance. There was a significant difference, however, in the 5-year survival rate of localized stage cervical cancer. Non-metropolitan women had a 5-year survival rate of 87.8%, significantly lower than the 91.3% rate for metropolitan women from 2000-2006.[37]

There are also differences in cervical cancer screening for urban and rural areas. Rural Non-Hispanic Whites were found to have a slightly lower prevalence of Pap smear testing than their urban counterparts. All rural women aged 35-49 also had a significantly lower prevalence of testing than their urban counterparts as well.[76]

CHAPTER III.

RESEARCH METHODS

3.1 Study Design

A late stage cancer diagnosis framework was adapted from Mobley *et.al* to provide justification for this study.[77]

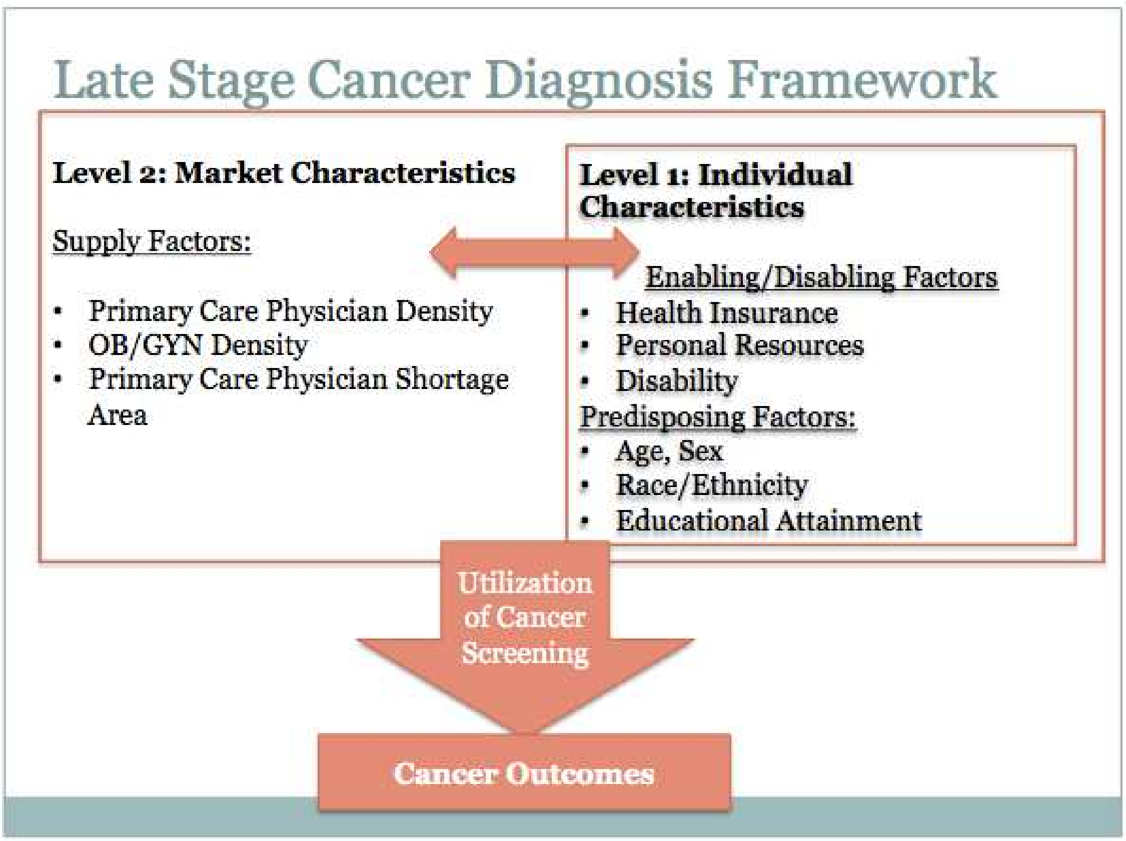

Figure 3.1. Late Stage Cancer Diagnosis Framework

Market supply factors include primary care physician density and OB/GYN density influence. Individual enabling or disabling factors include health insurance, disability, and personal resources. Other predisposing factors like race, age, and educational status are also individual characteristics of interest. These two levels (i.e., person and area level factors) may influence whether an individual utilizes cancer-screening services and in turn, can affect their cancer diagnosis outcome. This study is based on the assumptions that the level 1 and 2 characteristics are influential enough that their relationship with late-stage diagnosis will be able to be determined even if screening utilization is not taken into account.

This thesis used retrospective data from the South Carolina Central Cancer Registry to analyze primary care physician density and other related covariates and their relationship with cervical cancer stage at diagnosis. Descriptive statistics were used to depict various biological and socioeconomic risk factors for cervical cancer among women in South Carolina. ArcGIS was employed to provide visual geographic descriptions of the study population and their outcomes. Multivariate logistic regression models were run to assess the relationship between primary care physician density and late-stage cervical cancer diagnosis. The USC Institutional Review Board (IRB) approved this study on August 30, 2013 (Pro00028635).

3.2. Participants and Setting

3.2.1 Study Population

There were 2,188 incident cervical cancer cases identified from 2000-2010 in South Carolina. Data was obtained from the South Carolina Central Cancer Registry (SCCCR) through approval on April 3, 2014 from the Department of Health and Environmental Control IRB board (IRB14-003). The SCCCR is a division of the South Carolina Department of Health and Environmental Control and is a part of the North

American Association of Cancer Registries (NAACR). It is a population-based registry that collects cancer data for the entire state. As cancer is a reportable disease by law, the majority of cases are reported to SCCCR electronically by hospitals. Cases could also come from pathology labs, cancer treatment centers, and physicians' offices. The date of diagnosis, location, grade, and histology of tumor, as well as any treatment received, and vital status, is reported to SCCCR. Information about the patient's demographics like age, gender, race, and contact information are included in the case report. South Carolina residents that are diagnosed or treated out of state are still reported to the SCCCR as it has a reciprocal relationship with twenty surrounding states.[78] All invasive cervical cancer cases from 2000-2010 were included in the initial study population. Cases were excluded if they were classified as "unstaged". This led to 196 of the cervical cancer cases being excluded, which left 1,992 cases in the dataset. Due to missing age and race data, 1,950 cases were included in the multivariate analysis.

3.3. Variables

3.3.1. Outcome: Late-stage cervical cancer diagnosis

Cervical cancer cases were obtained from SCCCR, excluding any *in situ* cases, and those with a SEER grade of "regional"(n=689) or "distant" (n=203) were classified as a late-stage diagnosis. These were compared to early stage diagnosis or a SEER grade of "local" (n=1100).

3.3.2. Covariates*:* Rurality, Race, Age, Poverty, and Cancer Characteristics

Rurality was determined by census tract-level rural-urban commuting area (RUCA) codes. Created from US Census data, RUCA codes classify census tracts using measures of population density, urbanization, and daily commuting.[79] The RUCA classifications included in this study were urban and rural. Urban included codes for metropolitan areas, micropolitan areas with a primary or secondary flow within an urbanized area or urban cluster up to 49,999. Rural included all other areas. Due to the large time frame of this study, 2000 and 2010 RUCA codes were used. 2000 codes were assigned to cases diagnosed from 2000-2005 and 2010 codes were assigned to cases diagnosed from 2005-2010. Race was obtained from SCCCR and classified as White, Black, and Other. Age was also obtained from SCCCR as well as the cancer characteristics of each case. The cancer characteristics described for the study population were primary site, tumor grade, and histology. Poverty was obtained from SCCCR, which determines neighborhood census tract poverty level based on the 2000 US Census and the American Community Survey on five year basis. Poverty is categorized into <5%, 5-9.9%, 10-19.9%, ≥20%, and unknown. All cases assigned "unknown" for poverty (n=43) were manually determined using US Census American Community Survey estimates based on the case diagnosis year.

The South Carolina Central Cancer Registry does not collect information on all the known potential confounders and effect modifiers for cervical cancer thus leading to an incomplete list of potential confounders used in the actual analysis. The variable list of potential confounders used in this thesis is as follows:

- Race: Race was divided into White, Black and Other

- Poverty level: Poverty was categorized as <5%, 5-9.9%, 10-14.9% 15-19.9%, ≥20% by census tract
- Age: Age was treated as a categorical variable (<30, 30-49, 50-69, 70+ years)
- Census Tract Rurality: Urban/Rural was divided into urban and rural based on RUCA codes (Urban= <4.0, 4.1, 5.1,7.1,8.1, 10.1 Rural=4.0, 4.2, 5.0, 5.2, 6.1, 7.0- 7.4, 8.0-10.0, 10.2, >10.2)

SCCCR does not collect or does not have in completion: smoking status, educational status, household income, and insurance status. All of which would have liked to been included in analysis.

3.3.4. Primary Exposure: Primary Care Physician Density

Primary care physician density was calculated at the census tract and county level. There are currently 884 census tracts and 46 counties in South Carolina.[80] South Carolina medical licenses were used to determine primary care physician density by first filtering the licenses for only general practice, family practice, internal medicine, and obstetrics and gynecology specialties. As the study period encompasses ten years, lists for medical licenses were obtained for 2002, 2003, 2004 and 2009.The addresses provided on the medical licenses were geocoded and mapped at the census tract and county level using ArcGIS. For all addresses that listed a PO Box, the street address was manually searched for using the physician's name on Google. Using these maps, the number of primary care physicians in each census tract and county was calculated, divided by the total population, and multiplied by 100,000 to determine density. 2000 census population totals and census tract designations were used as SCCCR labels all cancer cases with 2000 census tract designations.

Cases diagnosed from 2000-2002 were assigned 2002 density levels, cases in 2003 were assigned 2003 density levels, cases in 2004-2006 were assigned 2004 density levels, and cases in 2007-2010 were assigned 2009 density levels. This was employed to help account for any temporality changes in primary care physician density that may have occurred from 2000 to 2010.

Density was categorized into two levels: none-low and moderate-high. For census tract primary care physician density per 100,000 the none-low designation=0, moderate-high=>0. County level primary care physician density per 100,000 for the none-low designation= <30, moderate-high =30-70. The county level cutoff was chosen at 30 physicians per 100,000 as it translated closely to the HSPA designation of 1 physician per 3,500.

3.4. Analysis

3.4.1 Geospatial Mapping

ArcGIS Version 10.1 (ESRI 2011. ArcGIS Desktop: Release 10. Redlands, CA: Environmental Systems Research Institute) was used to map the percentage of late-stage cervical cancer diagnoses at the county level for South Carolina. Primary care physician density was also mapped at the census tract and county levels.

3.5 Statistical Methods

Aim 1 examined differences between early and late stage cervical cancer using descriptive statistics including frequency counts and percentages. The variables compared were race, age, year of diagnosis, census tract rurality, poverty level, and primary cancer site. A chi-square test was used to assess statistical differences in early and late stage diagnosis for the aforementioned variables.

For Aim 2, we used logistic regression with stage at cervical cancer diagnosis as the outcome variable (0 = localized, 1= regional and distant stages). Logistic regression measures the relationship between a binary categorical dependent variable and one of more independent variables. The first part of the aim assessed the association between primary care physician density and late-stage cervical cancer diagnosis at the census tract level. The second part of the aim analyzed the association between primary care physician density and late-stage cervical cancer diagnosis at the county level. Significance was determined at the alpha=0.05 level.

Bivariate analysis for late-stage cervical cancer diagnosis as the dependent variable and primary care physician density was performed initially for both geographic levels of density. The next logistic regression model included all personal covariates and the primary exposure: race, age, and year of diagnosis as well as primary care physician density. The final logistic regression model was comprised of primary care physician density, race, age, year of diagnosis, poverty, and census tract rurality. Covariates that were not statistically significant at alpha=0.05, but epidemiologically relevant based on the literature were still included in the final model (see Equation 1.0 below). Data analysis was performed using SAS Version 9.4. (SAS Institute Inc., Cary, NC, USA)

(Equation 1.0)

Logit (P(Late Stage Cervical Cancer Diagnosis))= β_0 + β_1(PCP density) + β_2(race) + β_3(age) + β_4 (year of diagnosis) + β_5 (census tract rurality) + β_6 (poverty)

CHAPTER IV.

Effect of Primary Care Physician Density on Late Stage Cervical Cancer Diagnosis[1]

[1] Haanschoten, E. Eberth, J. Adams, A. Brandt, H. Moran, R. To be submitted to *Cancer*

INTRODUCTION

While great strides have been made in reducing cervical cancer incidence and mortality in the last 40 years, there are an estimated 12,360 incident cases and 4,020 deaths from cervical cancer in 2014 alone.[3] A crucial step in reducing cervical cancer morality is early detection.[9,17,57] Cases diagnosed late-stage have a five-year survival rate of approximately 12%. Conversely, early diagnosis cases have a five-year survival rate around 90%.[17]

For early detection to be possible, women must have access to appropriate care and utilize screening regularly. Only 64.9% of women who reported having no usual source of care had a Pap test within the past three years, this is much lower than the percentage reported for all women, 83%.[8] The density of primary care physicians (PCP) in one's geographic area can influence whether or not a women receives a Pap test, with women living in areas of higher PCP density reporting statistically higher rates of Pap tests than women living in lower areas of PCP density.[51] Increasing county level PCP density has also been associated with decreases in cervical cancer incidence and mortality.[23] Other cancers with strong screening programs like breast and colorectal cancer have previously shown relationships between PCP density and odds of late-stage diagnosis and cancer mortality.[22,24,47,48] Little is known however, about the relationship between PCP density and late-stage cervical cancer diagnosis at the census tract level. Previous literature has found that living in census tract that is classified as a medically underserved area (MUA) is a strong predictor of late stage diagnosis, but an entire state by tracts has not been examined as a whole.[17] Using census tract level PCP density should provide a more accurate representation of an individual's primary care access, as it is a smaller geographic level and more reflective of nearby PCP availability.

As South Carolina is 7th in the U.S. for cervical cancer mortality and 39th for PCP density, it provided an ideal environment for exploring this relationship[20,41]. South Carolina also ranks 13th in the nation for percentage of it's population living in a rural area.[21] Rurality has a large impact on access to care and can be detrimental in obtaining cervical cancer screening services.[81] South Carolina also has a large percentage of its counties reporting MUA and health care professional shortage areas (HPSA). In fact, only 2 counties out of 46 in South Carolina do not contain a MUA.[15] Eight counties had cervical cancer incidence rates 61% greater than the national rate with one county that reported an incidence rate 136% higher than the US.[31,32] (Figure 1) Another county in South Carolina had a mortality rate 117% greater than the US mortality rate for cervical cancer.[32] (Figure 2)

A late stage cancer diagnosis framework was adapted from Mobley *et.al* to provide justification for this study.[77] Market supply factors include primary care physician density and OB/GYN density influence. Individual enabling or disabling factors include health insurance, disability, and personal resources. Other predisposing factors like race, age, and educational status are also individual characteristics of interest. These two levels (i.e., person and area level factors) may influence whether an individual utilizes cancer-screening services and in turn, can affect their cancer diagnosis outcome. This study is based on the assumptions that the level 1 and 2 characteristics are influential enough that their relationship with late-stage diagnosis will be able to be determined even if screening utilization is not taken into account.

This study was conducted: (1) To describe the demographic and geographic differences between early and late stage cervical cancer diagnosis and the distribution of primary care physicians in South Carolina and (2) To determine if there is an association between PCP density and the risk of late stage diagnosis for cervical cancer in South Carolina at the census tract and county level. This study hypothesized that decreased primary care physician density will lead to increased odds of late-stage cervical cancer diagnosis.

METHODS

Data

Cervical cancer cases, excluding *in situ* cases, from 2000-2010 were retrieved from the South Carolina Central Cancer Registry (SCCCR), South Carolina's gold-rated statewide cancer registry, to assess the risk of late-stage diagnosis.[78] Information included in the case files along with specific cancer characteristics was race, age, year of diagnosis, and census tract poverty. Cases were linked by census tract to rural-urban commuting area (RUCA) codes, which classifies tracts using measures of population density, urbanization, and daily commuting.[79] As the study period spanned 10 years, 2000 and 2010 RUCA codes were used, with cases from 2000-05 assigned 2000 codes and cases from 2006-2010 assigned 2010 codes. 2000 census tract designations were used throughout the study period.

The primary outcome of interest, late stage diagnosis, was defined using Surveillance, Epidemiology and End Results (SEER) categories. Late stage diagnosis included "regional" and "distant" cases as compared to early stage diagnosis, which included “localized” cases. Stage was available for 1,992 cases (91.22%) of cases. Un-staged cases were excluded from analysis (n=192). The final sample consisted of all 1,992 women with known stage diagnosed with cervical cancer between 2000-2010 in SC. Due to missing age and race data, only 1,950 cases were included in the multivariate analysis.

Data for primary care physician density came from the South Carolina Medical Licensing Board.[82] Lists of all active medical licenses for 2002, 2003, 2004 and 2009 were obtained and then filtered for general practice, family practice, internal medicine, and obstetrics and gynecology specialties. Obstetricians and gynecologists (OB/GYNs) were included as primary care physicians due to the significant role they play in providing Pap tests.[51,53] To account for temporal changes in the supply of primary care physicians, cases diagnosed from 2000-2002 were assigned 2002 density levels, cases in 2003 were assigned 2003 density levels, cases in 2004-2006 were assigned 2004 density levels, and cases in 2007-2010 were assigned 2009 density levels. The addresses provided on the medical licenses were geocoded and mapped at the census tract and county level using ArcGIS Version 10.1 (ESRI 2011. ArcGIS Desktop: Release 10. Redlands, CA: Environmental Systems Research Institute) For all addresses that listed a P.O. Box, the street address was manually determined using an Internet search and the provider’s name. Density was calculated by dividing the total number of primary care physicians in each census tract and county by the respective 2000 and 2010 census population totals multiplied by 100,000. **Data Analysis** The percentages of late-stage cervical cancer cases were mapped using ArcGIS Version 10.1 (ESRI 2011. ArcGIS Desktop: Release 10. Redlands, CA: Environmental Systems Research Institute) at the county level. PCP density per 100,000 persons was also mapped at the census tract and county levels.

Differences between early and late stage cervical cancer cases were identified using descriptive statistics and Pearson's chi-square test with a 0.05 alpha level. The variables compared included race/ethnicity, age, year of diagnosis, urban/rural, poverty level, and primary cancer site.

The relationship between PCP density and the odds of late-stage diagnosis was examined using multivariate logistic regression. Three models were run for both the census tract and county level with late-stage diagnosis as the dependent variable. The first model consisted of only the bivariate relationship with PCP density. The second model included the primary exposure and all individual level covariates: race, age, and year of diagnosis as well as PCP density. The third model contained all of the variables from the second model plus covariates for poverty and urban/rural at the census tract level. Variables that were statistically insignificant, but epidemiologically relevant based on previous literature were retained in the final model. As the incidence of late stage diagnosis was greater than 10% and year of diagnosis was known, odds ratios were corrected to relative risks as a more appropriate interpretation of the magnitude of the association.[83]

As all cases living in the same census tract received the same poverty measure, there was concern that a multilevel model was more appropriate for analysis due to the hierarchical nature of the data. After further investigation, it was determined that both methods yielded very similar results and multivariate logistic regression was suitable for analysis.

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analysis, and ArcGIS Version 10.1 was used for geocoding and mapping purposes. Approval from the South Carolina IRB board was obtain August 30, 2013.

RESULTS

Of the 1,992 cervical cancer cases included in the descriptive analysis, 44.78% (n=892) were diagnosed late-stage. Table 1 shows the study demographics by stage of diagnosis. A greater percentage of African-American women made up the late-stage diagnosis cases (39.34%), compared to the percentage of African-American women that composed the early-stage cases (31.83%). However, the opposite was found for Whites. There were a higher percentage of cases among early-stage diagnosis (66.70%) than the percentage of cases among late-stage diagnosis (59.86%). This difference was statistically significant (p=<.0001). The median age of the study population was 48 years and there were statistically significant differences for late stage diagnosis (p=<.0001). Cases diagnosed early-stage were slightly younger at 44 years while late-stage cases were slightly older at 53 years. The highest percentage of cases diagnosed for both early and late-stage occurred among women aged 30-49 years old (53.82% and 42.04%, respectively). Women aged 50-69 made up a larger percentage of the late-stage cases (39.57%) than their percentage of the early-stage cases (28.00%). 2000-2003 had the lowest percentage of late-stage diagnosis cases and 2004-2007 had the highest. There were no statistically significant differences in late stage diagnosis noted between urban and rural areas (p=0.8645).

Mapping cervical cancer cases was not possible for census tracts, as only 6 tracts (out of 864 in SC) had greater than 10 cases over the time period. SCCCR suppresses tracts whose frequencies are less than 10. As expected, PCP density was highest in metropolitan areas and lowest in rural areas of the state (Figure 3, Figure 4). 426 of South Carolina's 864 (48.19%) census tracts had a PCP density of 0 per 100,000 persons. Five (10.87%) of the South Carolina's counties had less than 50 primary care physicians per 100,000 persons. Figure 5 shows the percentage of late-stage cases at the county level. 20 out of 46 (43.48%) counties had greater than 42% of the cervical cancer cases diagnosed as late-stage.

The results of the logistic regression models run are displayed in Table 2. Women living in census tracts with a primary care physician density greater than 0 per 100,000 were significantly less likely to be diagnosed late-stage compared to women who lived in tracts with a PCP density of 0 per 100,000. This was true for all three logistic regression models run. Similar results were seen at the county level where counties with greater than 30 PCPs per 100,000 were compared to those with less, but they were not statistically significant (Table 2). African Americans had significantly higher odds of being diagnosed late-stage than whites at both the census tract and county level. For both geographic levels, increasing age led to increased risk ratios for late-stage diagnosis. In the full model, cervical cancer cases diagnosed from 2008-2010 had a significant adjusted RR=1.547 (95% CI: 1.244, 1.611) for late-stage diagnosis as compared to cases from 2000-2003. Cases living in rural areas were slightly more likely to be diagnosed late-stage, but this was not found to be statistically significant (adjusted RR=1.007 95%CI: 0.952,1.055). The only proxy variable for socioeconomic status, census tract poverty, was significant in bivariate analysis for increased odds of late-stage diagnosis for women living in tracts with greater than 10% poverty compared to those in less than 5% poverty. Once included in a multivariate model, the increased odds were no longer significant.

DISCUSSION

This is the first investigation into the impact of census tract primary care physician density on late-stage cervical cancer diagnosis in South Carolina and any other state as a whole. As South Carolina is one of the nation's leaders in cervical cancer mortality, identifying areas that can improve cervical cancer survival is vital. South Carolina also has a large percentage of counties with MUAs, HPSAs and overall low primary care physician density, making it an ideal environment to study this relationship. Our analysis found that increased primary care physician density significantly decreased the risk of late-stage cervical cancer diagnosis when considered at the census tract level. While this association was not significant at the county level, the relative risk ratios were very similar. This suggests that access to care; specifically a primary care physician or an OB/GYN plays an impactful role in reducing late-stage cervical cancer diagnosis in South Carolina. Examining PCP density at the census tract allowed a more nuanced investigation into this relationship than other studies that only looked at the county level.[17,23]

Counties with highest percentage of late stage cases were often the counties with the lowest PCP density as was the case for Lee and Saluda counties. Lee County had 27.5% of its population below the poverty level from 2008-2012 and African Americans make up 63.9% of its citizens.[84] In Saluda County, however, 18.1% of its population was below poverty level from 2008-2012 and is 26.3% African American, but Saluda County is more rural than Lee County at 43.9 persons per square mile in 2010 compared to 46.9 persons.[84] Mapping revealed that counties with highest percentages of late stage cases were frequently surrounded by counties with the lowest percentages of late stage cases. Further comparison found that they also differ by PCP density. While there are other factors that likely contributed to the difference in stage diagnosis, PCP density is certainly worth full consideration.

Interestingly, counties with the highest percentage of late-stage cervical cancer diagnosis were not always the counties with highest mortality rates. Orangeburg, Florence, and Greenwood have some of the highest mortality rates in South Carolina, but all reported only approximately 42-53% of their cervical cancer cases as late stage. (Figure 2, Figure 5) Conversely, Laurens and Dorchester counties had some of the highest percentages of late-stage diagnosis in South Carolina, but reported low morality rates for 2000-2009.[31] Laurens County mortality rate had to be suppressed because it was so low. These differences may be an issue of access to care. Laurens and Dorchester are both adjacent to counties that have hospitals with gynecologic oncologists (i.e., Greenville, Spartanburg, and Charleston). Women in Orangeburg and Greenwood would have to travel much further to receive care from an equivocal source. This disparity in access to cervical cancer treatment may explain why the counties with the highest mortality rates were also not the counties with highest percentage of late-stage diagnosis. There are currently only 5 counties in South Carolina that have gynecologic oncology specialists (Greenville, Richland, Florence, Charleston, Spartanburg). This leaves thousands of women in South Carolina without easily accessible cervical cancer care if they were to need it.

A disproportionate number of African American women were affected by cervical cancer in this study population. African American women compose approximately 29% of the South Carolina female population, but make up 34.74% of all the cervical cancer cases from 2000-2010.[84] African American women were also more likely to be diagnosed late-stage, which falls in line with previous literature.[9,29,58] Interestingly, women diagnosed with cervical cancer after 2003 have a higher odds of late-stage diagnosis compared to those diagnosed from 2000-2003 with 2008-2010 cases having the highest risk. This may be a reflection of the decline in percentage of women that have had a regular Pap test, which has been seen in South Carolina and the United States as a whole.[85] Nationally, 67% of women aged 22-30 reported a Pap test in the last 3 years in 2010, down from 78.1% in 2000.[34] There was also an increase in this age group of women who reported never having a Pap test. Nine percent of women aged 22-30 in 2010 as compared to 6.6% in 2000.[34] One reason for this decline may be the changes in screening guidelines over this time period. The American Cancer Society (ACS), U.S. Preventive Services Task Force (USPSTF), and the American College of Obstetricians and Gynecologists (ACOG) all changed their cervical cancer screening guidelines, some multiple times, creating a confusing environment for women and their physicians.

This study was limited by a lack of socioeconomic and lifestyle factors included in analysis, especially smoking. Smoking is an influential risk factor for late-stage cervical cancer diagnosis[26,27,86] . It could not be included in the analysis due to lack of information from SCCCR. The only proxy variable for socioeconomic status, census tract poverty, was significant in bivariate analysis, but insignificant after adjustment for other covariates. Not knowing the insurance status of the study population was another limitation as it can play a substantial role in access to care and cervical cancer outcomes[2,56,65].

This research will be an important baseline and foundation when it comes to examining the effect of the Affordable Care Act on cervical cancer outcomes. The Affordable Care Act ensures that insurance companies provide reimbursement for women's preventive services including cervical cancer screening.[87] As demonstrated in the late stage cancer framework, monitoring the utilization of screening is important for the reduction of late stage diagnosis. As more women sign up for insurance through state and federal health exchanges, and more women have cervical cancer screening covered through their insurance plans, it will be important to further examine the relationship between primary care physician density, the utilization of screening services, and late-stage cervical cancer diagnosis.

Areas with low primary care physician densities and high late stage cervical cancer diagnosis should also be targets for clinical and policy interventions. These areas should be identified as potential sites for federally qualified health centers (FQHC) if they haven't been already. FQHCs can provide a safety net to communities that are otherwise lacking access to care.[88] Training on cervical cancer screening guidelines should be encouraged in all clinical practices as it has been through a recent upheaval and is often confusing.

In conclusion, we found that increasing the density of primary care physicians was associated with decreased risk of late stage cervical cancer diagnosis, especially at the census tract level. This study suggests the significant impact that primary care physicians and OB/GYNs can have in reducing the cervical cancer burden. Having access to care and being able to utilize screening services are important commodities in reducing late-stage diagnosis, which in turn can reduce the overall cervical cancer mortality burden. Screening interventions should target areas with low PCP density to maximize their effectiveness.

Table 4.1. Study Demographics by Stage

	Early (n=1100) 55.22%	**Late** (n=892) 44.78%	**P-value**
	%(n)	%(n)	
Race			**<.0001**
White	66.70 (723)	59.86 (528)	
Black	31.83 (345)	39.34 (347)	
Other	1.48 (16)	0.79 (7)	
Age			**<.0001**
<30	9.55 (105)	2.13 (19)	
30-49	53.82 (592)	42.04 (375)	
50-69	28.00(308)	39.57(353)	
70+	8.64 (95)	16.26 (145)	
Year of Dx			**<.0001**
2000-2003	44.45 (489)	30.27 (270)	
2004-2007	31.45 (346)	37.00 (330)	
2008-2010	24.09 (265)	32.74 (292)	
Poverty			**0.0010**
<5%	9.14 (98)	6.28 (55)	
5-9.9%	20.62 (221)	16.89 (148)	
10-19.9%	40.58 (434)	39.95 (350)	
≥20	29.66 (318)	36.87 (323)	
Urban/Rural			
Urban	78.08 (823)	78.41 (679)	0.8645
Rural	21.92 (231)	21.29 (187)	
Primary Site			**<.0001**
Endocervix	19.42 (214)	12.19 (109)	
Exocervix	1.18 (13)	1.34 (12)	
Overlap lesion cervix uteri	1.63 (18)	2.57 (23)	
Cervix uteri	77.77 (857)	83.89 (750)	

*Pearson's chi-square test

Table 4.2 The Odds of Late Stage Cervical Cancer Diagnosis

	Census Tract				County			
	Model 1	Model 2	Model 3	Corrected RR	Model 1	Model 2	Model 3	Corrected RR
Density*								
None-Low	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Moderate-High	**0.822 (0.686,0.984)**	**0.774 (0.641,0.936)**	**0.778 (0.641,0.945)**	**0.854 (0.748,0.996)**	0.884 (0.692,1.128)	0.823 (0.636,1.063)	0.843 (0.651,1.092)	0.845 (0.662,1.087)
Race								
White		Ref	Ref	Ref		Ref	Ref	Ref
Black		**1.292 (1.060,1.574)**	**1.234 (1.002,1.520)**	**1.08 (1.001,1.159)**		**1.283 (1.053,1.0564)**	1.228 (0.997,1.512)	1.081 (0.999,1.157)
Other		0.585 (0.231,1.480)	0.493 (0.186,1.313)	0.708 (0.363,1.016)		0.577 (0.227,1.466)	0.493 (0.185,1.313)	0.708 (0.362,1.106)
Age								
< 30		Ref	Ref	Ref		Ref	Ref	Ref
30-49		**3.351 (1.982,5.665)**	**3.513 (2.050,6.021)**	**3.335 (2.005,5.439)**		**3.282 (1.942,5.546)**	**3.435 (2.006,5.883)**	**3.266 (1.964,5.329)**
50-69		**6.101 (3.581,10.393)**	**6.293 (3.646,10.862)**	**5.655 (3.451,8.976)**		**6.005 (3.527,10.223)**	**6.184 (3.585,10.665)**	**5.569 (3.380,8.844)**

70+		**8.319 (4.682,14.781)**	**8.539 (4.737,15.392)**	**7.358 (4.388,11.781)**		**8.174 (4.603,14.513)**	**8.382 (4.653,15.096)**	**7.243 (4.317,11.610)**
Year of Dx								
2000-2003		Ref	Ref	Ref		Ref	Ref	Ref
2004-2007		**1.801 (1.441,2.251)**	**1.748 (1.391,2.195)**	**1.425 (1.244,1.612)**		**1.805 (1.445,2.255)**	**1.769 (1.412,2.217)**	**1.435 (1.347,1.740)**
2008-2010		**2.114 (1.691,2.674)**	**2.209 (1.391,2.195)**	**1.574 (1.244,1.611)**		**2.102 (1.662,2.658)**	**2.016 (1.585,2.565)**	**1.542 (1.347,1.710)**
Urban/Rural								
Urban			Ref	Ref			Ref	Ref
Rural			1.033 (0.809,1.318)	1.007 (0.952,1.055)			1.007 (0.790,1.284)	1.002 (0.946,1.050)
Poverty								
< 5%			Ref	Ref			Ref	Ref
5-9.9%			1.109 (0.734,1.677)	1.101 (0.747,1.609)			1.144 (0.758,1.726)	1.106 (0.770,1.651)
10-19.9%			1.250 (0.848,1.842)	1.231 (0.856,1.750)			1.321 (0.900,1.939)	1.295 (0.906,1.831)
>=20%			1.384 (0.809,2.063)	1.351 (0.818,1.934)			1.433 (0.963,2.132)	1.395 (0.965,1.990)

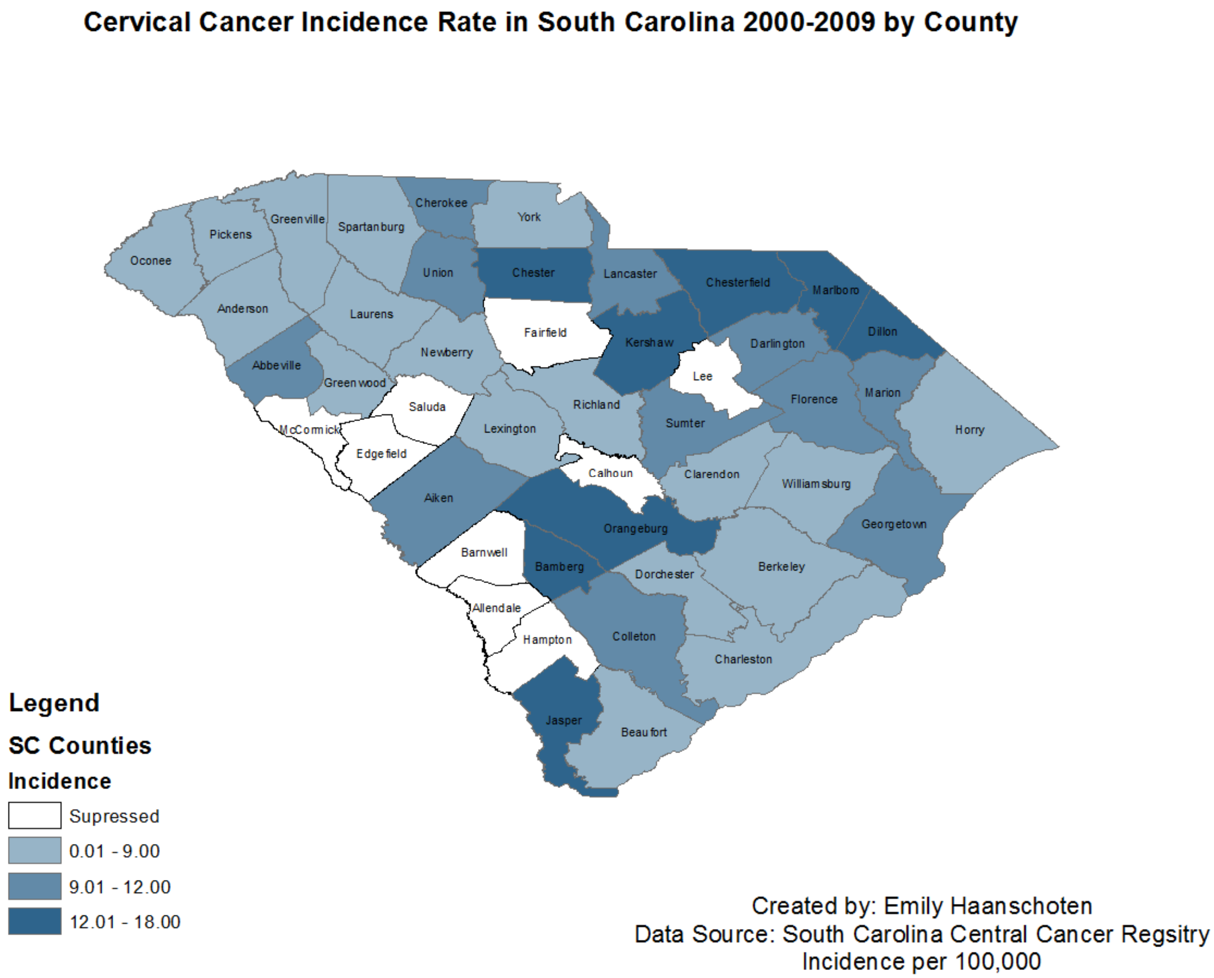

Figure 4.1. Cervical Cancer Incidence Rate per 100,000 persons in South Carolina by county, 2000-2009

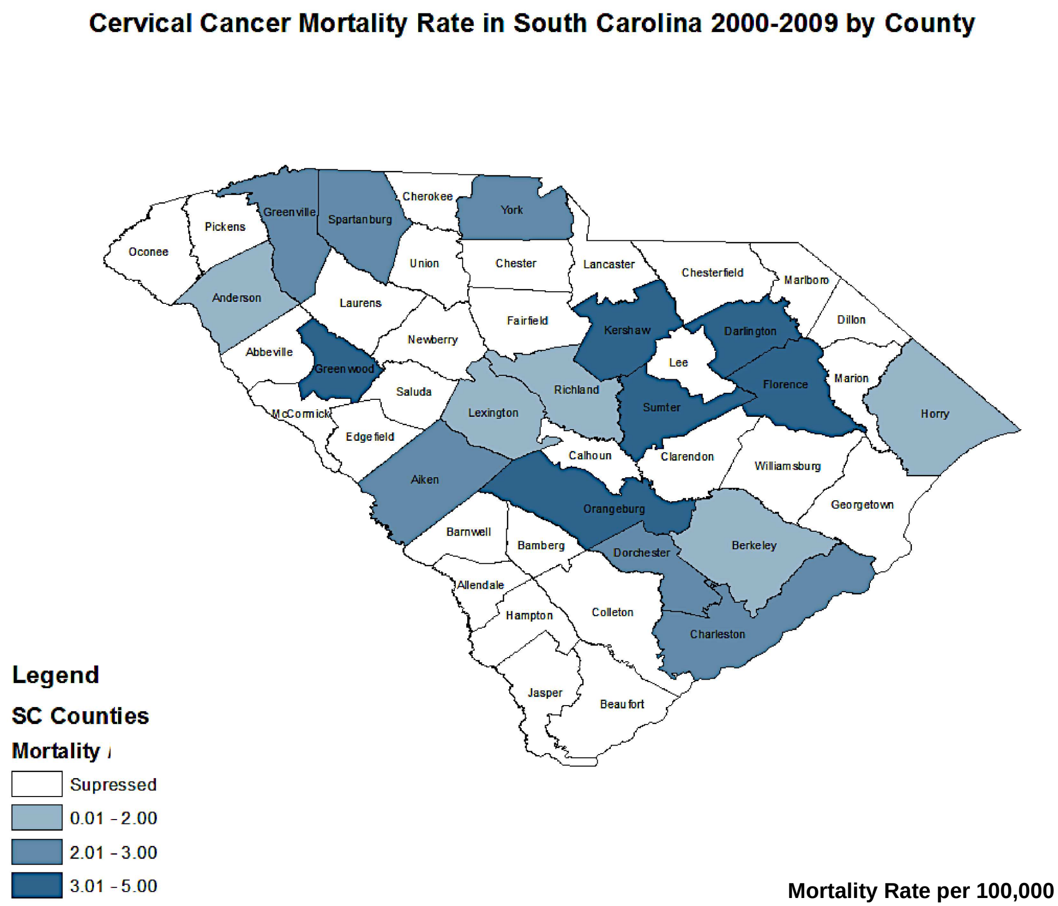

Figure 4.2. Cervical Cancer Mortality Rate per 100,000 in South Carolina by County, 2000-2009

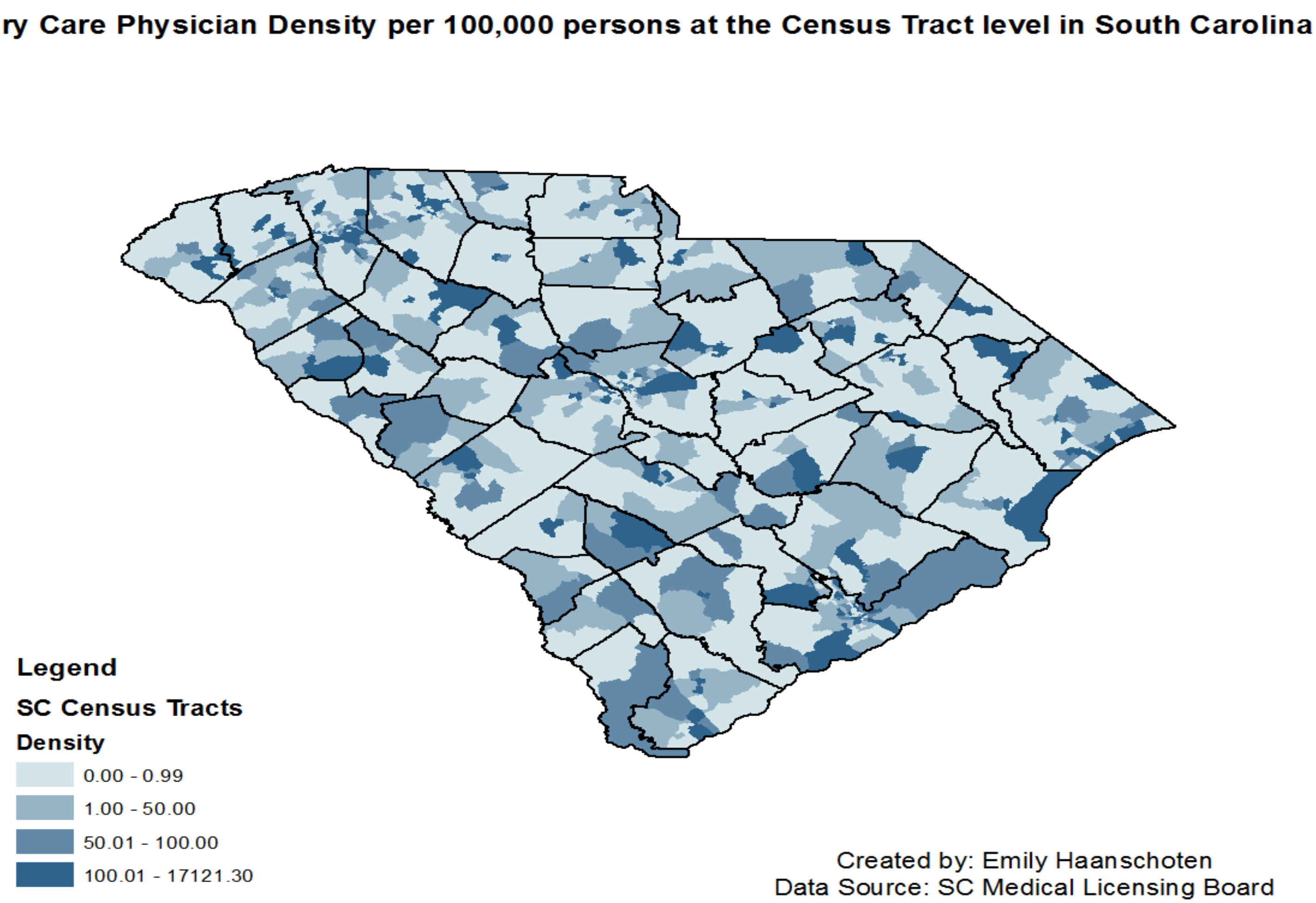

Figure 4.3. Primary Care Physician Density per 100,000 persons in South Carolina by census tract, 2009

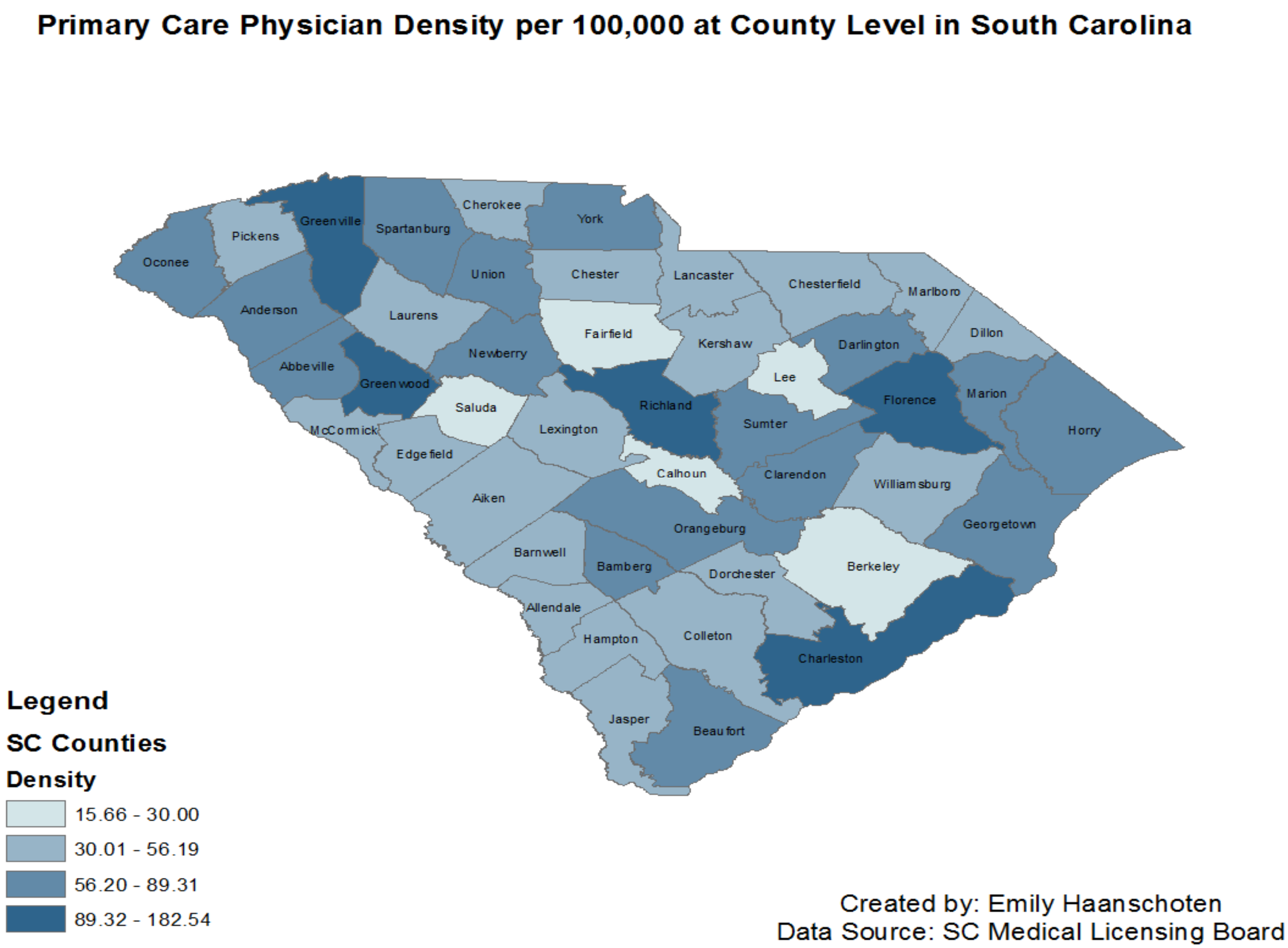

Figure 4.4. Primary Care Physician Density per 100,000 persons in South Carolina by county, 2009

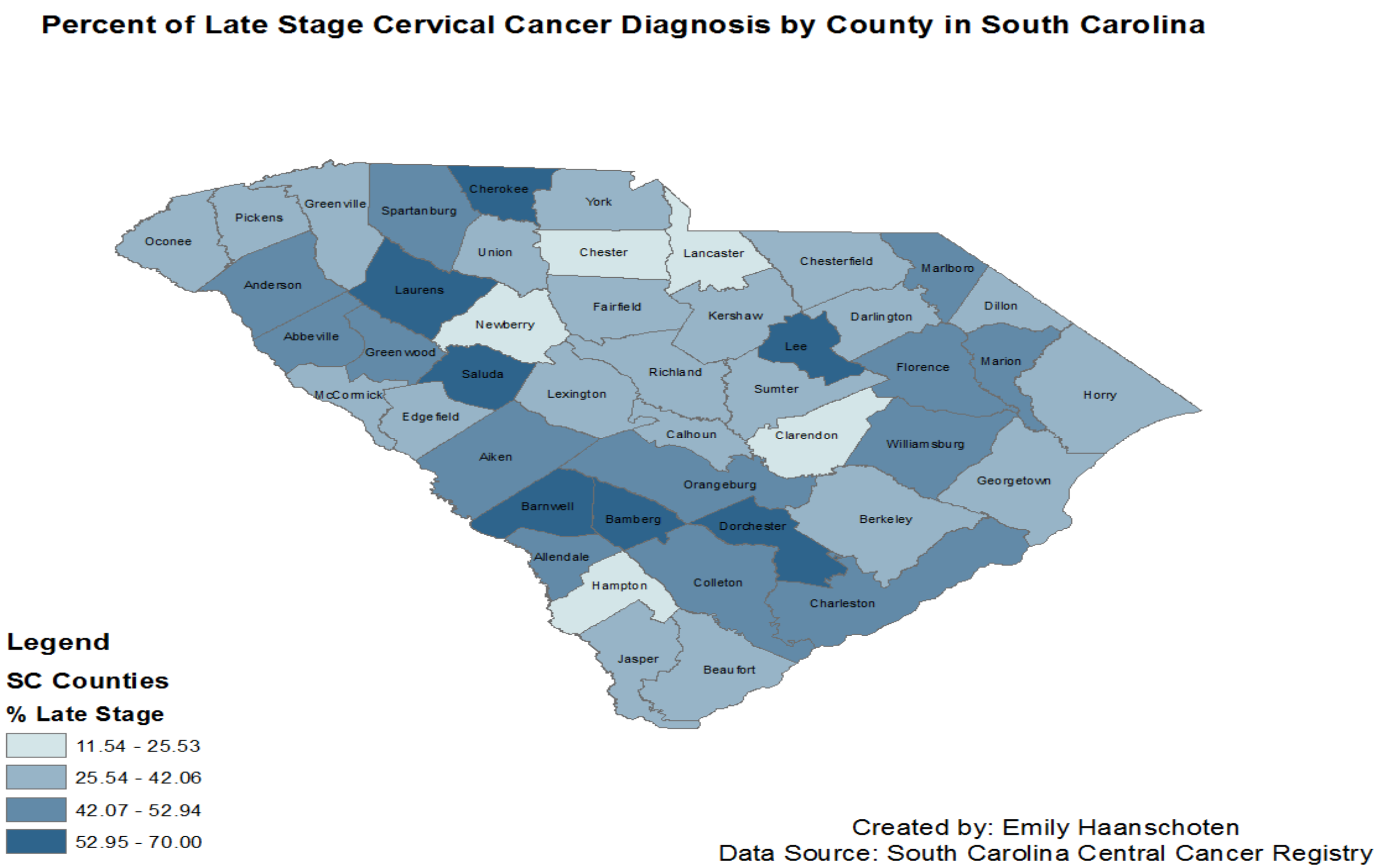

Figure 4.5. Percent of Late Stage Cervical Cancer Diagnosis in South Carolina by county, 2000-2010

CHAPTER V.

CONCLUSION

Summary of Results

In summary, census tracts with a primary care physician density greater than 0 per 100,000 persons have significant decreased odds of late stage cervical cancer diagnosis compared to census tracts with a primary care physician density of 0 per 100,000 persons. At the county level, similar decreased odds were also seen but it was not a statistically significant relationship. More recent years of diagnosis (2003 and later), older women, and African Americans all had significantly increased odds for late stage diagnosis at both geographic levels. Rural tracts and increased poverty also had elevated odds ratios for late stage diagnosis but were not significant in the multivariate models. Census tract poverty, however, significantly increased the odds of late stage diagnosis during bivariate analysis.

Significance of Findings

To date no other study has analyzed the impact of primary care physician density at the census tract level on the risk of late-stage cervical cancer diagnosis. All previous studies either examined county level densities or MUA tracts only and not an entire state.[17,23] This study found a deceased risk for late-stage diagnosis in census tracts and counties with "medium-high" PCP density as compared to areas with "none-low" PCP density. The association was statistically significant at the census tract level after adjusting for sex, age, year of diagnosis, urban/rural, and tract poverty. The inclusion of OB/GYNs as a part of primary care physician density is another unique factor of this study. OB/GYNs are highly influential in cervical cancer screening, but have not been previously included in PCP density analysis for late-stage cervical cancer diagnosis. Their addition is important to capture an accurate and complete picture of providers that provide cervical cancer screening.

As a state that is consistently ranked among the top of the charts in cervical cancer incidence and mortality, South Carolina has significant room for improvement. Reducing the number of cases diagnosed late-stage is one way to combat high cervical cancer mortality rates. As a state with a high rural population, a large number of HPSAs, and MUAs, and a large number of incident cases, South Carolina provides an ideal environment for studying the relationship between late-stage cervical cancer diagnosis and primary care physician density. South Carolina is also a state that rejected Medicaid expansion. An estimated 340,000 additional individuals would qualify for Medicaid if the state expanded the program or approximately 8.5% of South Carolina's total population and 40.5% of South Carolina's population below the poverty line.[80,89]

This research can be used to help focus cervical cancer screening interventions. Targeting areas low in PCP density and high in late-stage diagnosis with mobile clinics or other resources to increase screening access will hopefully decrease the frequency of late-stage cervical cancer diagnosis. Identifying the counties and census tracts with low PCP density is also important for influencing health policy that aims to reduce access to care disparities, especially through a cervical cancer lens. Programs like the Best Chance

Network that provides cervical cancer screening to low-income women can use this research to narrow in on areas that are most in need of their services.

Further Research

Further research should be conducted to assess whether this inverse relationship between PCP density and late-stage cervical cancer diagnosis is true across multiple states and regions in the United States. Additional analysis should include other covariates like smoking, marital status, insurance status, as well as education level or household income. Adding these variables to the analysis will help control for confounding and provide better indicators for socioeconomic status.

Further research should also examine the complete relationship in the late-stage cancer framework including the intermediary step of cervical cancer screening that was not able to be included in this study. This research should examine the relationship between primary care physician density, cervical cancer screening utilization, and their impacts on late-stage cervical cancer diagnosis. One way to accomplish this might be to inspect the effect of the Affordable Care Act on cervical cancer screening rates and how that ultimately affects late-stage cervical cancer diagnosis. The Affordable Care Act provides free preventive women's services like cervical cancer screening, which should help increase the number of women who do not receive Pap tests within the recommended guidelines. Monitoring and screening for cervical cancer is crucial in the reduction of late-stage cervical cancer diagnosis. This study provides a backdrop and baseline of information of which to build further research on and will be important as a reference for further research in late-stage cervical cancer diagnosis

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