The Journal
OF THE SOUTH CAROLINA MEDICAL ASSOCIATION

Cervical Cancer Disparities in South Carolina: An Update of Early Detection, Special Programs, Descriptive Epidemiology, and Emerging Directions

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South Carolina ranks eighth in the nation in cervical cancer mortality rates.[1] Cancer of the cervix (the lower and narrower portion of the uterus) is the ninth most common cancer among European American (EA) women and the fifth most common cancer among African American (AA) women in South Carolina.[1, 2] According to the most recent data, in South Carolina there were 220 new cases of cervical cancer in 2002 and 55 deaths in 2004.[1] These figures are alarming because cervical cancer is virtually 100 percent preventable if detected in precancerous stages. Disparities between EA and AA women are evident in terms of cervical cancer screening, incidence, and mortality. However, disparities in the main etiologic factor in the development of cervical cancer (i.e., human papillomavirus [HPV]) is unknown.

The purpose of this paper is to provide background information on cervical cancer; describe the distribution of disease in South Carolina as compared to the U.S.; discuss screening recommendations and emerging technologies; and focus on strategies to eliminate cervical cancer disparities among women in South Carolina.

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Etiology and Pathogenesis

Within the past 20 years, oncogenic (i.e., high-risk) genital HPV infection has been identified as the main etiological factor in the development of cervical cancer.[3,4] There are over 100 known types of HPV, of which 40 infect the genital tract; however, only 15 types are currently considered oncogenic (high-risk).[5] Infection with one of 13 types of oncogenic HPV DNA can be detected by a U.S. Food and Drug Administration (FDA)-approved method, Hybrid Capture II® (Digene Corporation, Gaithersburg MD). The HPV DNA test is approved for triage of women with equivocal Pap test results (i.e., atypical squamous cells of undetermined significance [ASCUS]) and for primary screening in conjunction with Pap tests for women 30 years and older.

Genital HPV infection is transmitted by skin-to-skin contact in the genital area.[6,7] Most HPV infections are transient, not persistent, and are resolved within nine months to a year.[8-10] Only persistent oncogenic HPV infection is a risk factor for cervical cancer.[11-13] HPV infection is very common among women and their partners. According to the Centers for Disease Control and Prevention (CDC), approximately 20 million people are currently infected with HPV in the U.S. At least 50 percent of sexually active men and women acquire genital HPV infection at some point in their lives. By age 50, at least 80% of women will have acquired genital HPV infection. About 6.2 million Americans get a new genital HPV infection each year while cervical cancer is very rare (<10,000 women per year).[14] Thus, HPV infection is necessary, but not sufficient to cause of invasive cervical cancer. Currently, the most effective preventive measure a woman can adopt to protect herself from cervical cancer is to have regular Pap tests, with HPV DNA testing as appropriate. Condoms have been shown to decrease the risk of cervical dysplasia and cervical cancer; however, until recently, the effectiveness of condoms in preventing transmission of HPV has been debated. A recent study by Winer et al. demonstrated that condoms are effective in preventing transmission of HPV.[15]

Additional co-factors are smoking, other sexually transmitted infections (especially chlamydia), immunosuppression (e.g., HIV infection, other chronic comorbid conditions, pregnancy, autoimmune disorders), and dietary factors.[9] Smoking may contribute to cervical cancer because it leads to the concentration of carcinogenic substances in the cervical mucus.[16] The hormones in oral contraceptives may contribute to the development of cervical cancer by modulating HPV gene expression in cervical cells.[17,18] In addition, socioeconomic factors have been identified as correlates of cervical cancer mortality, in particular.[19,20]

Descriptive Epidemiology

During the period 1997-2002, there were a total of 1,369 incident cases of cervical

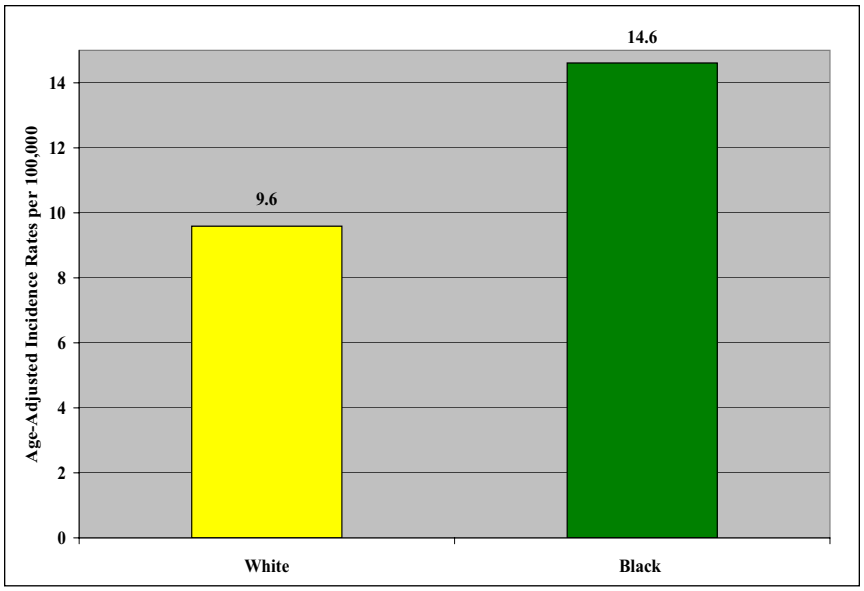

Figure 1. Cervical Cancer Age-Adjusted Incidence (1997-2002) Rates per 100,000 in SC by Race

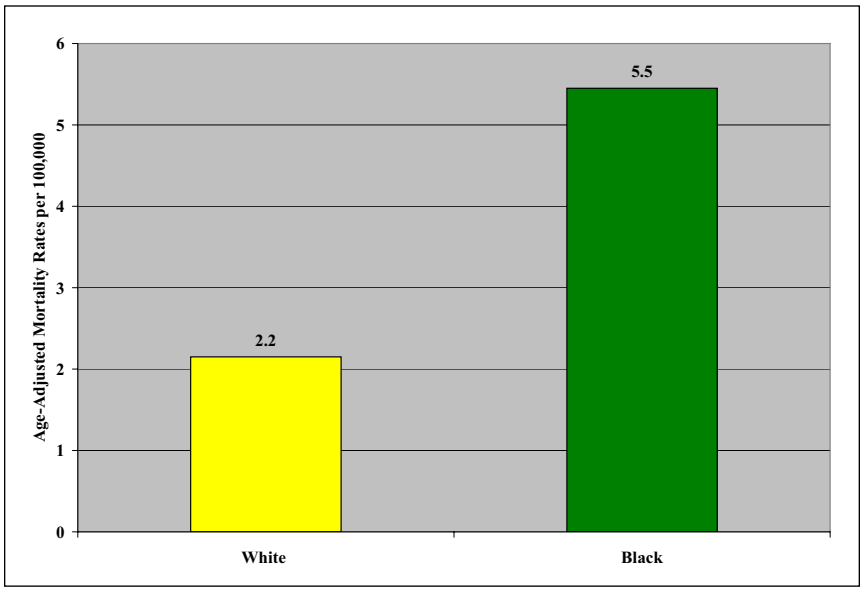

Figure 2. Cervical Cancer Age-Adjusted Mortality (1999-2004) Rates per 100,000 in SC by Race

cancer in South Carolina, of which 839 were among White (i.e., essentially EA) women and 493 among Black (i.e., essentially AA) women.[1] As shown in Figure 1, AA women had a much higher age-adjusted cervical cancer incidence rate than EA women (14.6 and 9.6 per 100,000, respectively).[1] During the period of 1999-2004, 402 women died of cervical cancer in South Carolina (208 White women and 187 Black women).[1] The racial disparity in mortality rates is alarming because cervical cancer is a preventable cancer that is detectable in precancerous stages. Black women have over two times the risk of dying from cervical cancer than White women (2.2 per 100,000 White women and 5.5 per 100,000 Black women) as shown in Figure 2.

Among all ages, regardless of race, most cervical cancer diagnoses are made at the local or earlier stage, demonstrating improvements in cervical cancer early detection. However, as shown in Figures 3 and 4, White women are more likely to be diagnosed at an early stage than Black women (64% local compared to 54%).[1] Unfortunately, it is not possible to tell whether there are differences by race and grade of dysplasia within South Carolina because these data are not currently collected by the South Carolina Central Cancer Registry (SCCCR). Observed disparities in cervical cancer incidence and mortality are particularly concerning, given that AA women are more likely to report having a Pap test in the previous three years than EA women and that AA women are more likely to be diagnosed with and die from cervical cancer.[21] Not only does this observation highlight the extreme importance of receiving both timely screening and follow-up care, but also that there are screening and follow-up differences by race that may ultimately determine differential survival rates by race.

Similar to most cancers, cervical cancer incidence and mortality rates increase with age, irrespective of race. Overall, women over the age of 30 are more likely to acquire and die from cervical cancer. Figure 5 shows the remarkably high incidence rates of cervical cancer among AA women in the 55 and older age group as compared to EA women.[1] As incidence rates increase among AA women with age, incidence rates decrease among EA counterparts. This is a disturbing trend and implicates older AA women as a high priority for cervical cancer screening programs in South Carolina.

Cervical cancer incidence and mortality rates vary among geographical regions. SAS/STAT® software, Version 9.1 was used to locate and map statistical differences in incidence and mortality rates.[22] Figures 6 and 7 highlight the counties where rates are significantly higher for AA women compared to the state rate for EA women.[1] Eight counties have significantly higher incidence rates for

AA women and 12 counties have significantly higher mortality rates for AA women, as compared to the state rate for EA women. County incidence rates are 1.5 to almost 3 times greater for AA women compared to the EA women state incidence rate. For example, in Orangeburg County, incidence rates are higher for EA women (16.6 per 100,000) and AA women (21.3 per 100,000) than most other counties in South Carolina.[1] Whereas, mortality rates are a more disconcerting 2.8 to 9.6 times greater for AA women compared to the EA women state rates. Only one county (Bamberg) shows significant differences in incidence for EA women. Differences in incidence among EA women may be most evident in rural areas. AA women living in rural areas are the least likely to receive cervical cancer screening in South Carolina. Mapping rates of incidence and mortality can help screening programs target specific areas of the state for early detection efforts. By screening high-risk populations, the number of cases diagnosed at early stages will increase and, in turn, decrease mortality.

Recommendations for Early Detection

In 2003, the American Cancer Society (ACS), American College of Obstetricians and Gynecologists (ACOG), National Cancer Institute (NCI), and the United States Preventive Services Task Force (USPSTF) changed their recommendations for cervical cancer screening to reflect the evolving nature of HPV DNA testing.[23-27] The new guidelines include age-specific recommendations and incorporate liquid-based cervical cell collection (e.g., ThinPrep®, Cytyc Corporation, Boxborough MA) and HPV DNA testing (Hybrid Capture II®).

Screening recommendations differ slightly among these entities; however, in general, the new guidelines are that all women should begin cervical cancer screening about three years after becoming sexually active or by age 21, whichever comes first. Annual screening should occur with traditional smear-method Pap tests or every two years using liquid-based cytology collection if the Pap test has been normal in the past. Then, beginning at age 30, women with three normal Pap test results in a row may be screened every two to three years with traditional or liquid-based testing. An option for women over 30 is to be screened every three years with either traditional or liquid-based testing, plus HPV DNA testing (i.e., DNAwithPap™, Digene Corporation, Gaithersburg MD). Women age 70 years or older with three or more normal Pap tests in a row and no abnormal Pap test results in the past ten years may choose to stop having cervical cancer screening.

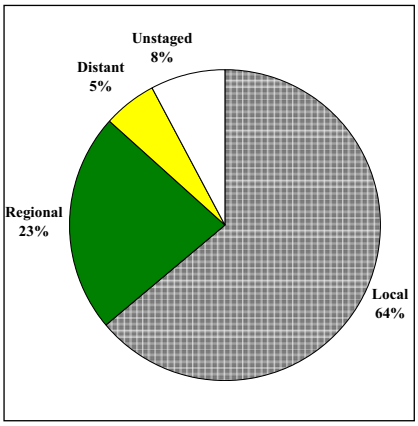

Figure 3. Cervical Cancer Stage at Diagnosis in SC among White Women, 1997-2002

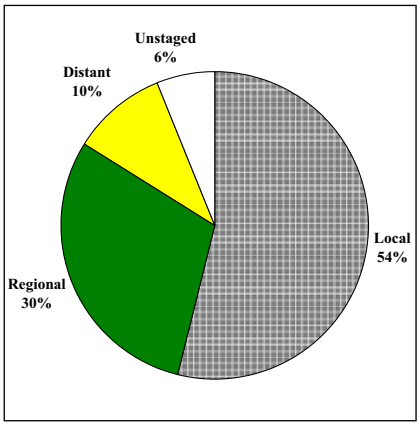

Figure 4. Cervical Cancer Stage at Diagnosis in SC among Black Women, 1997-2002

Special Programs in South Carolina

The South Carolina Breast and Cervical Cancer Early Detection Program, known as the Best Chance Network (BCN) is a joint effort of the South Carolina Department of Health and Environmental Control (SCDHEC) and ACS that is funded by the CDC. The BCN provides free cervical and breast cancer screening and treatment to underserved, income-eligible women between the ages of 47 and 64 years throughout South Carolina.

The South Carolina Medicaid Breast and Cervical Cancer Program began in 2001. The South Carolina Department of Health and Human Services (SCDHHS) entered into an agreement with BCN and SCDHEC to implement the provisions of the Breast and Cervical Cancer Prevention and Treatment Act of 2000. Most recently, the Department of Health and Human Services (DHHS), in partnership with SCDHEC and community advocates, worked successfully to attain one million dollars in state funds towards cervical and breast cancer treatment. This progress expands cancer treatment to women diagnosed outside the Best Chance Network. With this new funding, women with cervical dysplasia (CIN II, III and atypical hyperplasia) and cervical cancer will qualify for Medicaid to pay for their treatment if they are younger than 65 years of age; do not have insurance coverage that covers cervical cancer, including Medicare; and have a family income that is at or below 200% of the federal poverty level. Furthermore, by receiving treatment for cervical cancer under Medicaid, women receive full Medicaid benefits for the duration of the cervical cancer treatment. Recent changes to the program afford similar benefits to treat cervical dysplasia.

SCDHEC family planning services offers a yearly Pap test for women seeking family planning services. Medicaid eligibility or a sliding fee based on income is used to charge for services. Title X federal money is used to pay for services for women with no source of income and who are not Medicaid eligible.

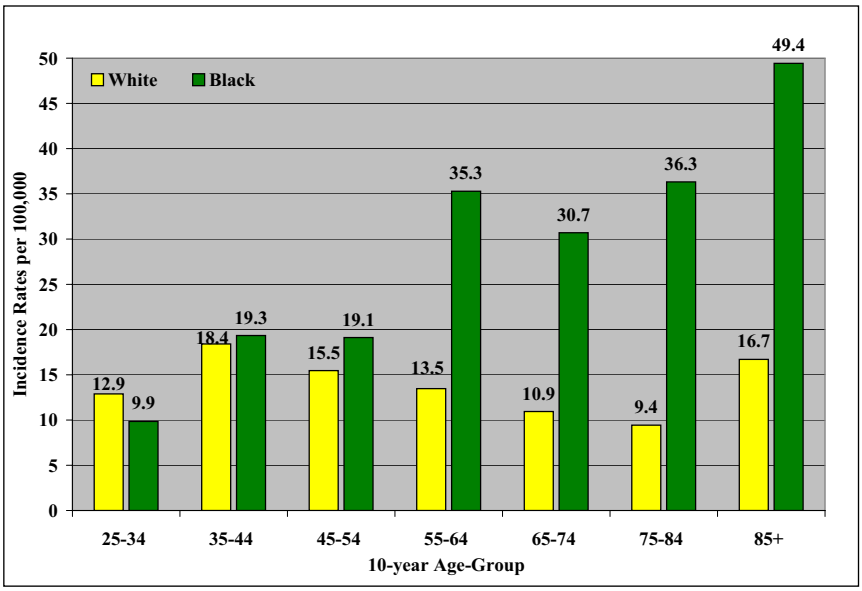

Figure 5. Cervical Cancer Age-Specific Incidence (1997-2002) Rates per 100,000 in SC by Race and 10-year age-groups

In addition, the Cancer Health Initiative which originated as a result of Palmetto Health's Certificate of Public Advantage (COPA), a contributory program which initiates community health outreach in the Midlands and Pickens County, provides cervical cancer screening to women 21-64 years who are below 200% of poverty and live in Richland, Lexington, and Fairfield Counties. Eligible women receive yearly screenings and are referred to a primary health care provider if an abnormal test result occurs. The Cancer Health Initiative makes financial arrangements with the follow-up physician.

Additional state, local, and regional medical centers, in collaboration with universities and/or private foundations, also offer screening programs for eligible women. Community health centers provide screening services based on a sliding fee scale, regardless of a woman's ability to pay. However, there are still women in South Carolina who are rarely or never screened due to complex factors, including limited access to care by virtue of inability to pay and geographic isolation. It should be noted that women also have a choice not to be screened.

Emerging Directions: HPV Vaccines

The widespread implementation and acceptance of the Pap test has been instrumental in dramatically reducing incidence and mortality rates among U.S. women; however, the potential for eradicating cervical cancer may lie in HPV vaccines, which have emerged as a new tool for preventing cervical cancer. Two vaccine candidates (Cervarix™ by GlaxoSmithKline and Gardasil® by Merck & Company) have undergone testing, and early results of these vaccines for some types of HPV have been promising and shown to be highly efficacious in short-term markers of cervical disease and genital warts.[28-32]

Merck & Company, Inc. has recently (June 2006) received FDA approval for Gardasil® which is a prophylactic, quadrivalent vaccine for two types of high-risk HPV (16 and 18) and two types of low-risk HPV (6 and 11).[33,34] The CDC Advisory Committee on Immunization Practices (ACIP) voted to recommend that the newly licensed vaccine, Gardasil®, be routinely given to girls when they are 11-12 years old.[35] The ACIP recommendation also allows for vaccination of girls beginning at nine years old as well as vaccination of girls and women 13-26 years old.[35] Gardasil® is comprised of virus-like particles (VLPs) that essentially mimic or copy the included HPV types to stimulate antibody development and subsequent immune response if the host is exposed without the risk of cervical disease and genital warts.[36] Gardasil ® will be given in three doses at zero, two, and six months to females in the target age range.[36] The most commonly reported side effect was pain and soreness at the injection site, which is a common side effect of injections.[36] At this time, the duration of protection and need for booster doses are being determined in ongoing clinical trials.[36]

Recommendations for administering the vaccine to adolescent girls and young women has changed the target audience of cervical cancer prevention and control efforts to include parents, adolescents, and pediatricians in addition to the specialists (e.g., gynecologists, internal medicine) and primary care providers who have been involved for years. The potential of the HPV vaccine lies in its acceptability by the target audience, as well as the ability of the public health and medical systems to effectively deliver the vaccine.[32,37-44] This is a current source of debate.[45-48] Even with the implementation of HPV vaccines, cervical cancer screening will remain a priority.

Focus on Eliminating Cervical Cancer Disparities

The NCI released a report in 2005 documenting that excess cervical cancer mortality is a marker for limited access to care and an indicator of poor health.[19, 49] Although South Carolina is not featured in the report, the state shares many of the characteristics of the areas of the U.S. included in the report. Much is known about the etiological relationship of genital HPV infection to cervical dysplasia and cervical cancer, yet little is delivered to the general population as demonstrated by limited HPV knowledge, lack of available educational interventions, and excess cervical cancer mortality.[50-60]

Strategies for improving access through outreach, services, and navigation; information and communication; research; and collaborations, partnerships, and advocacy are identified. Ongoing work in South Carolina is consistent with these recommendations and others.[53] In addition, the following efforts are needed to address cervical cancer disparities, according to the report by Freeman et al.[19]

Increasing knowledge and understanding of cervical cancer and HPV among women in South Carolina are important components of changing cervical cancer incidence and mortality rates.[61,62] Educational challenges emerge as a critical issue in this state, due to the complexity of HPV infection, low literacy rates (and likely low health literacy), potential stigma of a sexually transmitted infection linked to cervical cancer, and interaction of psychosocial and emotional responses to diagnosis. It is evident that many women do not understand cervical cancer screening (e.g., Pap test tests only for cervical cancer, importance of follow-up care for abnormal results), the meaning of an abnormal Pap test result, and causes of an abnormal result (especially the role of HPV).[9,50-52,54] Culturally sensitive and linguistically appropriate educational programs and interventions to increase knowledge and understanding are needed.[61,63-65] Increased understanding among women and the public in general will be crucial to the acceptance of HPV vaccines as a prevention tool for cervical cancer.[37,46]

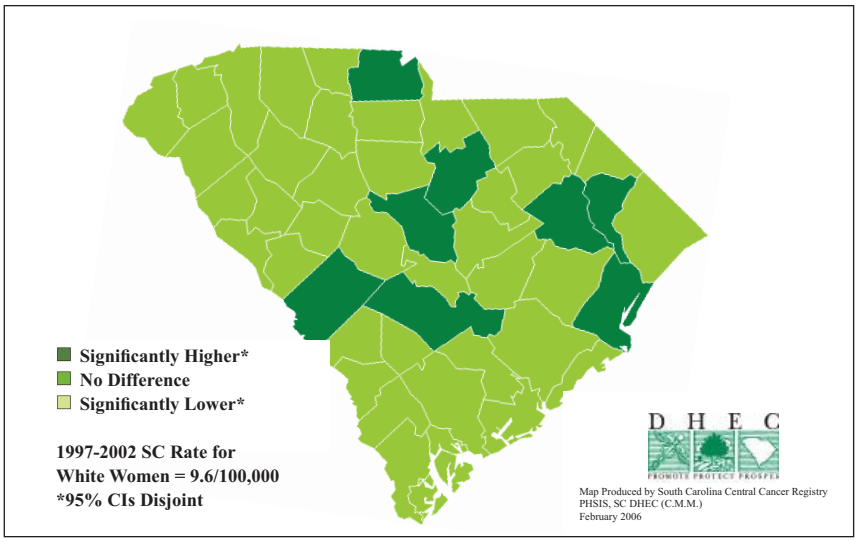

Figure 6. South Carolina Cervical Cancer: Comparison of the Age-Adjusted, County-Specific Incidence Rate for Black Women vs. the Age-Adjusted, State-Specific Incidence Rate for White Women (1997-2002)

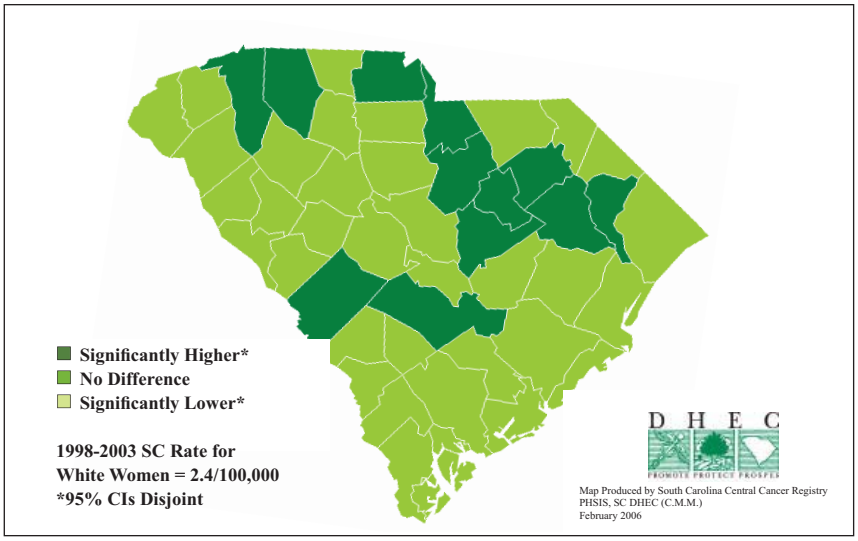

Figure 7. South Carolina Cervical Cancer: Comparison of the Age-Adjusted, County-Specific Mortality Rate for Black Women vs. the Age-Adjusted, State-Specific Mortality Rate for White Women (1998-2003)

In addition to educational programs, there is a need for ongoing professional education to keep clinicians abreast of the most current scientific information, clinical techniques, and patients' needs.[66-68] For example, education and implementation of the ALTS trial recommendations, such as use of the liquid-based ThinPrep® collection technique could be beneficial to both clinicians and patients.[69] Liquid-based collection may be more accurate, cost-effective, and will allow for additional research when more clinics are using it as a primary screening method,[70-74] although additional, independent research is needed to confirm and a recent review contradicted the value of liquid-based cytology.[75] In South Carolina, routine use of HPV DNA testing as a means for determining follow-up care for abnormal Pap test results (i.e., ASCUS results) is not known. Preliminary studies indicate irregular use of HPV DNA testing.[76] If the patient tests positive for oncogenic HPV, then colposcopy is warranted for diagnostic purposes. HPV DNA testing is underutilized in follow-up care for women with equivocal results, such as ASCUS. HPV DNA testing of ASCUS results could save women from having unnecessary colposcopies. We see the need to provide educational information and messages to clinicians about uses of HPV DNA testing as part of cervical cancer screening and how best to provide this information to their patients. In addition, we need to

increase knowledge and understanding of Gardasil® and other emerging technologies related to cervical cancer (such as serum markers of IGF-II).[77-80]

Lastly, it would benefit South Carolina to explore a reporting data system that includes data on preneoplastic lesions that are more likely to develop into cervical cancer (biopsy-confirmed high grade cervical dysplasia). Ideally, the SCCCR would collect these biopsy-confirmed dysplasia cases. A registry of high-grade cervical dysplasia could be quite beneficial in tracking the incidence and progression (or regression) of cervical dysplasia to reduce cervical cancer mortality. Such a registry could be linked to a navigator approach that has shown promise among women with breast cancer to provide linkages and facilitation to clinical systems.

Summary

Through careful examination of cervical cancer incidence and mortality rates and current resources available in South Carolina, we have identified research and intervention priorities related to cervical cancer that would best serve the women of this state. Mortality rates due to cervical cancer are largely explained by the lack of early detection among women rarely and never screened and non-adherence to recommended follow-up care of cervical dysplasia; however, other factors less well explained are determinants of observed disparities between AA and EA women. Efforts are underway to implement strategies recommended by the NCI to eliminate cervical cancer disparities through improved efforts to reach out to rarely and never-screened women and prepare health care providers for implementation of HPV vaccines.

Acknowledgment:

We would like to acknowledge funding of the South Carolina Cancer Disparities Community Network through grant number 1 U01 CA114601-01 from the National Cancer Institute (Community Networks Program). We would like to acknowledge the South Carolina Central Cancer Registry (SCCCR) for the state cancer incidence and mortality data provided. The SCCCR is funded by the CDC National Program of Cancer Registries, cooperative agreement number U55CCU421931, and SC Department of Health and Environmental Control.

We would like to thank Shalanda Bynum, MS, Justin H. Smith, BS, Sara Wagner, MSPH, and Marcie Wright, MPH for their editorial assistance in the preparation of this manuscript.

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