SOUTH CAROLINA
CERVICAL CANCER STUDY

A Report on the Status of Cervical Cancer Prevention and Control

Report to the Governor and the General Assembly

Proviso 9.50
Proviso 9.48

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October 2005

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Special thanks to Ms. Joyce Hallenbeck, MPH and Ms. Catishia Mosley, MSPH for their assistance with the preparation of this report.

Executive Summary

No woman in the United States should develop or die from cervical cancer. This disease is highly preventable through regular screening and essentially treatable if detected early.

In South Carolina (SC), cervical cancer is the 12th leading cause of cancer death among women.[1] Although cervical cancer incidence and mortality rates have decreased in the last thirty years, these rates remain high in SC, particularly among racial/ethnic minorities, relative to other states. In SC, Black women have a 60% higher incidence rate of cervical cancer and are 2.6 times more likely to die of cervical cancer than White women.[1]

Infection with oncogenic (cancer causing) or "high risk" human papillomavirus (HPV) is the primary risk factor for cervical cancer. However, oncogenic HPV infection alone is not sufficient for cervical cancer development. HPV infection is extremely common among the sexually active population (up to 80% of people will have HPV at some point in their lives) and most will not know that they have it. The majority of infections will "clear" within a year without any type of intervention (i.e., treatment). Women with persistent oncogenic HPV infection are at significant risk for cervical dysplasia (cellular changes that may be precancerous), which may lead to cervical cancer if not identified through screening and appropriately treated.

Risk factors besides oncogenic HPV exist for cervical cancer. Modifiable risk factors include: sexual behaviors, smoking, diet and immune-suppression, while non –modifiable risk factors are age, race and socioeconomic status. The combination of these risk factors with persistent oncogenic HPV infection can lead to cervical dysplasia and subsequently cervical

cancer if not detected early through Pap tests and adherence to recommended follow up protocols.

Early detection of cervical dysplasia is important in preventing cervical cancer. Given that Pap test screening rates in SC are above the national average, it is disturbing that SC ranks eighth in the nation for cervical cancer mortality. These facts suggest that other underlying, implicit factors may be contributing to the public health problem in SC. While Pap tests are very necessary to detect pre-cancerous conditions, follow-up adherence for abnormal test results are equally essential to detect and effectively treated cervical dysplasia, thereby avoiding the development of cervical cancer. Cervical cancer cases most often occur among women who are never or rarely screened and among women who delay or do not adhere to the recommended follow-up plan of care.

Both conventional and newer cervical cancer screening technologies (such as liquid-based methods) allow for early detection of cellular changes. While the use of liquid-based Pap tests may increase the number of false positives among women without decreasing cervical cancer mortality, it is, however, critical for SC to take advantage of the high sensitivity of liquid-based Pap tests. SC must ensure all women with abnormal cellular changes are screened and identified (true positives). SC must use the newest effective technologies to reduce the state's high cervical cancer incidence and mortality rates.

Use of HPV DNA testing as a triage strategy for ambiguous Pap test results plays an important role in the diagnosis and management of cervical dysplasia. The HPV DNA test can identify women who may need immediate follow-up because they have oncogenic HPV versus women who are not oncogenic HPV carriers (low risk) with dysplasia. HPV DNA testing can determine the need for annual follow-up due to persistent oncogenic HPV infection.

Introduction of the HPV DNA test into routine screening standards has moved the recommended screening intervals from an annual Pap test to three-year cycles for women who are low risk and older than 30 years with a history of normal Pap tests for three consecutive years.

Liquid-based Pap tests have improved sampling procedures and appear to be cost and time effective when sampling among populations with a high prevalence of oncogenic HPV infection or cervical dysplasia. The greatest benefit of liquid-based Pap tests is that it allows for use of cells in the original sample for reflexive HPV DNA testing as well as use of the original sample to confirm abnormal cells of undetermined significance in cytology results. Liquid-based testing allows for one sample/one office visit for a triage of tests to determine the significance of abnormal results. Conventional Pap test methods allow for only one reading and are more prone to sensitivity sampling errors. Upon abnormal results, conventional methods require a second office visit for either visual inspection through a technique called colposcopy, a second sample collection to confirm cytology results, and/or HPV DNA testing.

Challenges to follow up adherence are complex and multi-faceted. Barriers exist from physical limitations such as transportation, to competing life priorities such as lack of sick leave and childcare, as well as monetary and psychosocial effects. The complexities associated with the message of diagnosis with oncogenic HPV infection, cervical dysplasia and cervical cancer are also overwhelming for many patients. Therefore, it is imperative for medical and public health professionals to communicate effective, clear and concise educational messages with women on the importance of Pap tests, implications and meaning of abnormal results, and adherence to follow-up and treatment. The primary message for development and communication is that knowledge of oncogenic HPV prevention is critical, and that screening and adherence to recommended follow-up care are paramount to the prevention of cervical

cancer. The language of cervical cancer and oncogenic HPV is complex and inherently confusing, thus there is a need for the development of concise, culturally, and linguistically appropriate educational messages that effectively convey the essential information needed by the patients. Anti-HPV vaccines are currently in development and may be introduced in clinical practice during 2006. The vaccines show great promise for being able to eventually eliminate HPV (16 and 18) infection and dramatically decrease cervical cancer rates. However, even under the best conditions, it will take generations before the impact of the anti-HPV vaccine is felt; therefore, efforts to detect and treat cervical dysplasia and cervical cancer at early stages must continue and intensify.[2] While other oncogenic types are prevalent in the U.S., the vaccines currently being developed target only two of the oncogenic types of HPV (16 and 18), which are responsible for the majority of cases of cervical cancer in the United States.

Cervical cancer prevention is a priority for South Carolina. Significant local research has been conducted and continues. Researchers from the medical universities, school of public health, state and local health departments, and private entities collaborate on a continual basis to understand the problem of cervical cancer in South Carolina.

RECOMMENDATIONS

1. Institute liquid-based Pap testing among DHEC Family Planning Clinics according to the findings of current assessments regarding the feasibility of instituting liquid-based testing in these clinical settings. The liquid-based test will increase the number of true positives thereby improving the ability to identify new cases (incidence) and prevent deaths (mortality).
2. Institute FDA-approved HPV DNA testing among DHEC Family Planning Clinics.

3. Initiate state funding to develop and enhance cervical cancer screening programs for women who are not eligible for screening through current programs due to lack of program capacity or federal program eligibility criteria.
4. Improve state surveillance and research funding to investigate the complex barriers to care faced by SC women in access to screening programs and support for follow-up care procedures and treatment of severe cervical dysplasia or cancer.
5. Explore existing partnerships to educate health care professionals and women utilizing research-based materials and prevention technologies on HPV and cervical cancer.

Introduction

SC Cervical Cancer Study Group Responds to Proviso 9.50

In response to legislative Proviso 9.50, the Department of Health and Environmental Control convened an expert study group to address the issues of cervical cancer in South Carolina (Appendix A). Members of the study group comprised researchers, faculty and staff from the Medical University of South Carolina (MUSC), University of South Carolina (USC) School of Medicine, USC Arnold School of Public Health, USC Prevention Research Center, DHEC Health District staff, DHEC Division of Cancer Prevention and Control, DHEC South Carolina Central Cancer Registry, and external consultants. Each member of the study group was formally invited to participate by Dr. Lisa Waddell, DHEC Deputy Commissioner of Health Services. During the course of the year, the study group met five times in person and regularly communicated via email and telephone. This report is a result of the study group's analysis of the cervical cancer problem in South Carolina.

During its preparation for this report, the study group communicated with a pharmaceutical firm that is involved in cervical cancer research and in the development of a HPV vaccine. A representative of the firm subsequently met with the group and provided updated information regarding vaccine development.

During the development of this report, the study group communicated with the South Carolina Legislative Womens Caucus and participated in an event held by the Caucus with guest speaker Christine Baze, a cervical cancer survivor. For this event, DHEC developed an informational brochure on the current cervical cancer activities and status of the proviso report (Appendix B).

Cervical Cancer Statement of Public Health Significance

More than 60 years ago, the American Cancer Society first recommended that women undergo cervical smears for the early detection of cervical cancer. In the years immediately following this recommendation, clear declines in the number of women dying from cervical cancer were observed, especially in areas where rates of cervical cancer screening were high. The introduction of the Pap test as a cervical cancer screening test has been touted as one of the 10 greatest public health achievements of the 20th century. However, cervical cancer is the 12th leading cause of cancer death among South Carolina women and the large racial gaps for cervical cancer mortality indicate that the benefits of cervical cancer screening and care are not unequally distributed. Black women in South Carolina are more than twice as likely to die from cervical cancer as are White women. Additionally, no woman should die, let alone develop from cervical cancer when it can be effectively detected early and successfully treated at the cervical dysplasia stage.

The identification of risk factors for cervical cancer has also progressed. In the past 20 years, oncogenic human papillomavirus (HPV), a common sexually transmitted virus, has been identified as the main etiologic factor in the development of cervical cancer. Oncogenic HPV is not a singular "cause" of cervical cancer. This and other co-factors play an important role in the development of cervical dysplasia and cancer. However, while oncogenic (cancer-causing) HPV infection is extremely common, cervical cancer in comparison is rare.

Methods of early detection are more sophisticated today and the Pap test is only one component of cervical cancer screening. The strong link between oncogenic HPV and cervical cancer risk has led to the development of methods to test for HPV. A clinical laboratory test for HPV DNA has been recommended as a triage strategy for women who have abnormal Pap test

results (i.e., reflex testing) and as a primary screening tool for women aged 30 years and older. These improvements have modified screening guidelines for early detection. In fact, annual cervical cancer screening may soon be replaced with biennial and triennial screening for women who are determined to be at low risk as determined by multiple consecutive normal tests.

Despite advances in the technology for early diagnosis of cervical cancer, racial disparities persist among women in the United States and especially, in South Carolina. This public health challenge exists despite the fact that screening tests have been available for the past 60 years and cervical cancer can be prevented when detected early. Both HPV and cervical dysplasia (low and high grade cellular changes) often present communication challenges because of women's psychosocial responses and low levels of health literacy. The language of cervical cancer and oncogenic HPV is complex and inherently confusing, thus there is a need for the development of concise, culturally, and linguistically appropriate educational messages that effectively convey the essential information needed by the patients.

In the near future, a vaccine for some types of HPV will be available. However, in order for people to be receptive to the vaccine, education of both the public and health care practitioners is needed to convey accurate information about the vaccine, its effectiveness, and the benefits and the relative risks associated with vaccination.

The public health challenges in South Carolina are clear. We must, therefore,

1. Work to prevent cervical cancer through screening.
2. Work to eliminate racial disparities in cervical cancer.
3. Reach out to rarely and never screened women.
4. Promote and assure culturally and linguistically appropriate educational messages for patients and health care professionals.
5. Develop support and facilitative systems to ensure timely follow-up of abnormal Pap test results.
6. Identify and remove the financial, geographic, educational, structural and cultural barriers that contribute to racial disparities in cervical cancer.

These are important steps to promote cervical cancer prevention, reduce incidence and mortality rates, and increase public awareness of the causes, prevention and early detection of this disease.

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WHAT IS CERVICAL CANCER?

Etiology and Pathogenesis

HPV is the most common sexually-transmitted viral infection. Oncogenic (cancer causing) types of HPV are a major cause of cervical cancer as demonstrated by human cervical cells growing indefinitely in culture.[3-9] Hundreds of HPV types have been isolated; however, only relatively few are oncogenic. Oncogenic HPV types 16 and 18 are most prevalent in the United States, while other oncogenic types are more common in other parts of the world.

HPV is thought to infect cells at the base of the lining of the cervix, primarily in the zone where the cell types transform from one type to another in the cervix. This is a very dynamic area in the cervix, where the epithelium changes architecture on a periodic basis. While cells at the base of the cervical lining are the target of infection, virus production occurs in the cells at the top layers of the lining. The ability of HPV to transform normal cells to cancer cells resides primarily in the viral proteins that exhibit a wide variety of activities and interact with numerous cellular proteins. The best characterized activities of these proteins are their interactions that lead to degradation of cellular proteins that suppress tumor cells. The HPV proteins function to re-start DNA synthesis in cervical cells and therefore "prime" the host cell to produce viral DNA and ultimately more virus. Cancer development is thought to begin when the expression of viral proteins becomes unregulated, usually through integration of the viral DNA into the host cell genes. Unregulated expression of viral proteins produces a marked loss in tumor suppressor genes, and allows the cells to produce their DNA and arrest growth in normal cells. While normal cells have a finite life span in culture, cervical cells transformed with HPV16 or HPV18

are capable of growing indefinitely, and gradually acquiring resistance to growth inhibitors that control the growth of normal cells. One can easily envision how HPV in the cervical epithelium could trigger the growth of clonal cells with extended life span, which are resistant to the growth control mechanisms that ensure the stability and architecture of the tissue, leading to dysplasia. Given the fact that they are genetically unstable, these cells are more susceptible than normal cells to further carcinogenic stimuli, and may progress to cancer, under the right conditions.

It is now well accepted that oncogenic HPV infection is necessary to trigger the sequence of events that lead to cervical cancer. However, oncogenic HPV alone is not sufficient to "drive" the process all the way to cancer. Even in culture, progression of HPV16 transformed cells to malignancy requires a long and complicated series of selection steps, long term culturing, and treatment with additional carcinogens. Other host and environmental factors, many of which remain poorly defined, play pivotal roles in cervical cancer development.[10-14]

A couple of the key questions in the field, of particular significance from a clinical point of view, are: "What exactly are those additional factors, and how do they work?" Until anti-HPV vaccines become available, the best method for the detection and prevention of cervical cancer is to screen for cervical dysplasia (by the Pap test) and/or to screen for oncogenic HPV infection. The combined use of Pap test and HPV DNA testing have the potential of identifying virtually all women at risk of developing invasive disease. This is true especially if screening includes typing the HPV DNA, and distinguishing between transient and persistent infection.

Risk Factors for Cervical Cancer

In considering risk factors for cervical cancer, it is useful to recognize there are two types of risk factors, modifiable risk factors such as smoking and sexual behaviors, and non-modifiable factors such as increasing age and race. In general, a woman can lower her lifetime risk for cervical cancer by limiting exposure to oncogenic HPV through sexual contact (e.g., abstaining from sexual activity, using condoms, mutual monogamy), having regular Pap tests and HPV DNA tests as appropriate, avoiding cigarette smoking, and eating a nutritional diet (especially one that is high in antioxidants and antioxidant-rich foods).

Persistent infection by oncogenic, genital HPV is the primary risk factor for cervical cancer; however, oncogenic HPV alone is not sufficient to cause cervical cancer. Suspected co-modifiable risk factors include diet, immunosuppression (e.g., pregnancy, other acute and chronic conditions), cigarette smoking, and sexual history (early age at first sex, multiple partners). Research also suggests oral contraceptive use as a potential risk factor.

Modifiable Risk Factors for Cervical Cancer

Sexual Behaviors and HPV

In the past 20 years, oncogenic HPV has been identified as the main, etiological risk factor for cervical cancer.[3-9] Currently, up to 15 types of HPV are classified as oncogenic, or high-risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. Of these 15 strains of oncogenic HPV, 13 are detectable by HPV DNA testing. Continental geographic differences in the distribution of oncogenic HPV types and cervical cancer exist.[15]

HPV transmission and infection occurs through sexual genital contact. There are no noticeable symptoms of oncogenic HPV in males or females. Infections are often clinically silent,

producing no symptoms or discomfort. The only way to know if a woman has oncogenic HPV is through HPV DNA testing, as recommended and approved.

HPV is very common. The prevalence of HPV infection is higher in women than men. Oncogenic HPV infection clears within a year or so in most cases, and clinical persistence of the virus is a relatively rare occurrence. It was recently shown that the women in whom oncogenic HPV infection persists are those who are truly at risk for cervical cancer. However, even among women with persistent oncogenic HPV infection, cervical dysplasia does not always occur indicating that other factors are involved in the pathogenesis of cervical cancer.

ORAL CONTRACEPTIVE USE

No definitive evidence exists linking the use of oral contraceptives with cervical cancer. However, there is some statistical evidence that long-term oral contraceptive (OC) use may slightly increase the risk of cervical cancer.[16-19] The increased risk may be due to non-use of barrier methods of contraception because of reliance on OCs. On the other hand, OC users may be more likely to have a precancerous or early stage cervical cancer diagnosis because users may receive more Pap tests due to yearly screenings for prescription purposes. Therefore, perhaps these women are tested more regularly.[20] Research is underway to determine whether OC use or the likelihood of non-use of barrier methods is the cause for increased risk. The American Cancer Society believes that a woman and her clinician should consider whether the benefits of using OCs outweigh this very slight potential risk.

DIET

Women with poor diets may be at increased risk for cervical cancer.[21, 22] Much of the initial evidence focuses on antioxidants or anti-oxidant rich foods.[23],[24] Diets low in fruits and vegetables are associated with an increased risk of cervical cancer and several other

cancers.[24] Diets high in vegetables may increase the rate of oncogenic HPV remission.[25] Eating a balanced diet with folic acid and vitamins C and E can also increase the body's ability to fight off oncogenic HPV infection[26], and may help to reverse or delay the process of dysplasia.

SMOKING

Smoking exposes the body to many carcinogens that affect more parts of the body than the lungs. Smoking contributes to a weakening of the immune system[26] and tobacco by-products have been found in cervical mucosa in women who smoke.[21] One recent study has found that women who smoke and have oncogenic HPV with abnormal Pap tests were more likely to be diagnosed later with precancerous or severe cervical dysplasia (CIN III) or cancer compared to nonsmokers.[27] Researchers believe that these substances damage the DNA of cervical cells and may contribute to the development of cervical cancer.[28, 29] Smokers are about twice as likely as nonsmokers to get cervical cancer; however, the exact biologic relationship of smoking to oncogenic HPV is less clear.[21]

IMMUNOSUPPRESSION

Increased risk for developing cervical cancer is related to the immune response, which is lower among women who have HIV, are pregnant, or have other immune-compromised conditions.

Scientists believe that the immune system is important in destroying cancer cells and slowing their growth and spread to other parts of the body.[13] In women with HIV infection, cervical dysplasia might develop into an invasive cancer more rapidly. This also may be true among women who are pregnant and women who are immune-compromised because of other conditions (e.g., organ transplant recipients).[26]

CHLAMYDIA INFECTION

Research has shown previous or current Chlamydia (a sexually transmitted bacterial infection of the male and female genitalia) infection(s) result in an increased risk of developing cervical cancer.[30, 31] An increased prevalence of oncogenic HPV types (e.g., 16) among women with a history of Chlamydia infection(s) has also been demonstrated.[32] A recent study examining concurrent HPV and Chlamydia infections in young women found that the association between Chlamydia infections and cervical cancer may be due to an effect of Chlamydia infection persistence on HPV.[33]

NON-MODIFIABLE RISK FACTORS FOR CERVICAL CANCER

AGE

The average age of women newly diagnosed with cervical cancer is between 50 and 55 years.[21] The risk of developing this cancer is very low among girls younger than 15, and risk increases between the late teens and mid-30s. However, cervical cancer can affect young women in their teens and 20s. As with all cancers, age is an important risk factor. Age may affect cervical cancer development uniquely because women under the age of 30 are more likely to have oncogenic HPV, but cervical cancer is more common in women over age 30.[26] Many older women do not realize that it is important for them to continue having regular Pap tests until they meet the recommended guidelines of three normal Pap tests after age 65 yrs.[26] As women age, their bodies encounter compromised immunity making them more susceptible to persistent oncogenic HPV infection that may develop into cervical cancer. Reduced rates of Pap test screening among older women who have never received a Pap test or who have a recent abnormal Pap test history leads to a later stage cervical cancer at diagnosis, resulting in higher mortality rates.

A new oncogenic HPV infection is uncommon among women of this age group. Women with persistent infection or history of abnormal tests should continue screening. To avoid low rates of cervical cancer screening among older women, clinicians need to limit their biases based on patients' age, ability to pay, and race to ensure adequate access for older women.[34]

RACE

Several racial groups have cervical cancer death rates that are higher than the U.S. average. Incidence rates for cervical cancer among Blacks are 65 percent higher than for White women.[35] The death rate for cervical cancer in Black women is over twice the national average.[21, 35] Hispanics and American Indians also have cervical cancer death rates that are above average. Factors related to race and ethnicity are related to other risk factors. Higher death rates may be related to decreased or irregular access to preventive and early detection services, such as Pap tests, and reduced adherence to follow-up diagnostic procedures and treatment.[35] For instance, up to 80 percent of minority women fail to obtain follow-up care for abnormal Pap tests.[35] Disruptions in the continuity of care and a lack of resources for ethnic minority women to receive follow-up are important factors that increase risk for cervical cancer.

LOW SOCIOECONOMIC STATUS (SES)

Low socioeconomic status is a risk factor for cervical cancer and could be viewed as modifiable or non-modifiable.[35] Low SES women's higher risk can be attributed to a higher prevalence of other risk factors and lack of timely follow-up for abnormal Pap tests. [35] Low SES has also been related to poor dietary practices.[21] Rates of smoking are also higher among women who have financial challenges.[36] Financially challenged women do not have ready access to adequate health care services and may not always qualify for government screening programs.

Descriptive Epidemiology

INCIDENCE AND MORTALITY

The patterns of new cervical cancer cases and cervical cancer deaths in SC and the Southern region of the country are higher than the total US rates. Cervical cancer is the ninth most commonly diagnosed cancer among women in SC. Overall, cervical cancer occurs more often among South Carolina women than it does in the nation. South Carolina's cervical cancer incidence rate is 24 percent higher than the US incidence rate (11.4 per 100,000 versus 8.4 per 100,000 respectively).[1] Although SC's cervical cancer incidence rate is slightly higher than the nation, a report published by the South Carolina Cancer Alliance reports that a South Carolina woman's risk of getting cervical cancer is similar to the rest of the nation.[37]

In 2001, cervical cancer was the 15th leading cause of cancer death among women in the US and the 12th leading cause of cancer death in SC's women. As a state, South Carolina ranks eighth in the nation for cervical cancer mortality. SC's mortality rate is 37% higher than that of the United States (3.7 per 100,000 versus 2.7 per 100,000, respectively). The risk of dying from the disease is far greater among South Carolina women than women in the rest of the nation.[37] The burden of cervical cancer mortality is not felt by South Carolina alone, but by the Southern region of the United States.[38] Cervical cancer mortality rates in the Southern region exceed the national rate by 15% (3.1 for South vs. 2.7 for US).[38]

RACIAL DISPARITIES

Race plays an important role in describing cervical cancer. Huge gaps exist in both incidence and mortality between Whites and Blacks. Black women in both the US and SC are more often diagnosed with and die from cervical cancer than compared to Whites. In SC, Black women have 61% excess incidence of cervical cancer compared to Whites. Cervical cancer was

the fifth most commonly diagnosed cancer among Black females, but the tenth most commonly diagnosed cancer among Whites. Although the gap remains wide, the racial difference in incidence has narrowed over time. Incidence rates among Blacks have declined each year by almost 5% since 1973.[39] However, huge gaps continue to exist in the United States and South Carolina. No geographic patterns by race appear when comparing SC county incidence compared to US rates (See Figures 1A and 1B).[1]

The racial gap of cervical cancer appears as women age (See Figure 2). The incidence rate of cervical cancer is similar for younger White and Black women. The gap begins to appear after age 55 years of age, with the largest differences appearing among Black women age 65 and older.

In addition to having higher incidence rates, a higher percentage of Black women are diagnosed with late stage (regional or distant spread of disease) cervical cancer compared to White women (40 percent versus 29 percent) (See Figures 3A and 3B). The increased percentage of late stage diagnosis among Black women contributes to increased mortality.

More than twice as many Black women die from cervical cancer as do White women. Black females in the Southern region of the nation have the highest mortality rate in the nation (5.2 per 100,000 compared to 4.8 per 100,000, respectively).[38] Among the Southern states, South Carolina's black females have especially poor outcomes. South Carolina ranks seventh in the nation for cervical cancer mortality among Black females.[1] The cervical cancer mortality rate among Black women in SC is 40% higher than US mortality rates and almost 30% higher than the Southern rate. [1] No geographic patterns by race appear when looking at SC county mortality compared to US rates (See Figures 4A and 4B).[1]

RESEARCH-BASED STRATEGIES FOR

CERVICAL CANCER PREVENTION AND CONTROL

Cervical Cancer Prevention

Most of the preventive actions for the development of cervical cancer that a woman can take are related to avoiding exposure to oncogenic HPV infection, improving her immune response, and most importantly participating in regular screening and follow-up recommendations. Avoiding exposure may not be plausible given the fact that the great majority (~80%) of sexually active adults will encounter some type of HPV (oncogenic or non-oncogenic) infection at some point in their lives. It is not known how much protection condoms provide against HPV. In 2000, the U.S. Department of Health and Human Services as instructed by the US Congress conducted a thorough review of literature regarding scientific evidence of condom use as a prevention strategy for acquiring and transmitting sexually transmitted infections. Due to insufficient evidence, the reviewers were not able to determine the effectiveness of condoms in preventing genital HPV infection in men or women. Studies since then have shown that condom use is associated with reduced cervical dysplasia rates and clearance of HPV infection in women and regression of HPV lesions in men. [40-42]

A woman's immune system is an important determinant of how oncogenic HPV infection will affect her. A healthy immune system is necessary to effectively clear detectable levels of oncogenic HPV infection and avoid persistent infection, which may lead to the development of cancerous cells. Several methods of improving an individual's immune system have been documented. These include getting enough sleep, eating a healthy diet, managing stress, not

smoking, avoiding excess use of illicit drugs and alcohol, and preventing other acute and chronic conditions.

It has been demonstrated by research that the majority of cervical cancer cases occur among women with little or no screening history using the Pap test or among women without appropriate follow-up for abnormal Pap test results.[43] The success of the Pap test, both conventional and newer technologies, has been due to the test's sensitivity to detect cervical dysplasia for treatment. Successful treatment of these lesions can prevent the development of invasive cancer.

LIQUID-BASED COLLECTION VERSUS CONVENTIONAL SMEAR METHODS

The best method for the detection and prevention of cervical cancer is to screen for precursor lesions by the Pap test and/or to screen for oncogenic HPV infection. In the past, cervical cancer screening recommendations have been that all women who have been sexually active or who are 18 years of age and older should have annual Pap tests and pelvic exams. Physician recommendation of Pap test is an important predictor of screening.[25] These guidelines have recently (2003) been updated to reflect the evolving nature of liquid-based collection of cervical cells and HPV DNA testing.[44-49] The new guidelines include age-specific screening recommendations, incorporating technological advancements, and extending the screening interval among women with normal results on routine screening.

Screening guidelines differ slightly among authorities (see Appendix B). 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 conventional Pap tests using the smear method or every two years using liquid-based cytology collection. 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. A reasonable option for women over 30 is to be screened every three years with either conventional or liquid-based testing, plus HPV DNA testing. Current screening recommendations do not support Pap test screening for women over the age of 65 years with a history of normal test results.

While there is agreement that liquid-based Pap testing is more sensitive than conventional Pap tests, liquid-based Pap tests have increased the likelihood of generating false positives test

results. Increased false positives may result in increased secondary screening and follow up costs

HPV DNA TESTING

Although the prevalence of oncogenic HPV infection has increased among younger women, Pap test utilization has decreased cervical cancer incidence and mortality rates over time by early detection and follow-up on cervical dysplasia. Procedures of follow-up on abnormal Pap test results can be potentially improved through new technology. The combined use of conventional or liquid-based Pap tests and HPV DNA testing has the potential of identifying virtually all women at risk of developing invasive disease. The combination testing can help distinguish between transient and persistent oncogenic HPV infections which is important in identifying women at risk of developing precancerous disease or cervical cancer.[50, 51] Without HPV DNA testing results, unnecessary additional procedures (e.g. visual inspection of the cervix called colposcopy and biopsy) may be performed on women who are at low risk of developing persistent cervical dysplasia and/or cancer. The number of women that undergo colposcopy after repeated positive Pap tests (with or without added HPV DNA testing) is still far greater than the number of women who are truly at risk for invasive disease. In fact, most Cervical Intraepithelial Neoplasia (CIN) I (mild), II, (moderate) and even CIN III (severe) lesions either persist or regress naturally.[51] Therefore, the identification of susceptibility to oncogenic HPV-mediated transformation would help in the management of women who are most likely to regress, and would help identify women at the highest risk of progression who may need more aggressive treatment. Such testing would contribute significantly to both the efficacy and the cost effectiveness of cervical cancer screening programs.

Concept of Adherence versus Compliance

The terms "adherence" and "compliance" have been used interchangeably in the literature and have similar definitions. These terms describe the "extent to which a person follows or conforms to a prescribed medical care plan" or "the extent to which a person's behavior (in terms of returning for further medical care) corresponds with the clinical recommendation."[52, 53] Patients whose behavior does not match provider's recommendations frequently become labeled as "non-compliant," a term which limits our understanding of the patient's point of view and is restrictive to the establishment of therapeutic relationships. Today more updated terms such as "adherence" and "empowerment" are used. These terms evoke patients' participation and involvement in their own health care. Through open and effective dialogue, the clinician can establish the patient's level of understanding of the situation and the need for adherence.[54]

Cervical Cancer Screening Adherence

Cervical cancer cases most often occur among women who are never or rarely screened plus among women who do not adhere to necessary follow-up appointments. Given inconsistent definitions and associated follow-up recommendations, rates of reported adherence vary widely. Reported adherence rates range from 15% to 88% but are compounded by additional factors including different study populations, settings/locations, research foci, and evaluation outcomes.[55-62]

Improved adherence to screening recommendations and follow-up of abnormal results are necessary prerequisites to a reduction in the incidence of cervical cancer. Factors influencing

patient adherence include provider factors, provider system factors and patient characteristics. Published studies have investigated several population groups to determine specific areas of screening and adherence need.[62-70] From these studies, women at risk for not adhering to screening guidelines are more likely to be older, lack a regular provider, belong to a minority group, lack higher levels of education, be less acculturated when they are immigrants, have weaker social networks, and have less faith in the efficacy of cancer prevention.[71] Conclusions drawn from adherence studies on why these women do not adhere are often multifaceted and complex. Such complexities include health beliefs, cultural differences, religious beliefs, anxiety, coping styles, lack of transportation, insurance, cancer fears and fatalism, life circumstances, level of disease.[72, 73] All these need to be considered when developing systems that enable women to obtain cervical cancer screening and appropriate follow-up care.

Current interventions to improve adherence most often target specific barriers such as telephone appointment reminders when time between appointments is lengthy, bus passes for those with transportation difficulties, educational brochures, videos to enhance understanding and importance of care, and cash incentives for low-income women. Though these interventions have shown varying degrees of success, the majority have shown only modest improvements in adherence rates.

A system-wide organization of care that addresses these multiple factors and associated barriers has yet to be developed. Lack of a statewide systematic follow-up program for all women with abnormal Pap tests impedes identification of those who are adequately screened, but may have underlying cervical disease. There is a need to re-examine the processes by which low-income and rural women obtain care so that valuable public health resources can be more

effectively utilized. The women at highest risk for cervical cancer in South Carolina may be those who are least likely to adhere to recommendations for both initial screening and follow-up.

EDUCATIONAL NEEDS OF HEALTH CARE PRACTITIONERS

A key evidence based strategy to impact cervical cancer early detection is targeted education of health care practitioners. Knowledge of the current screening guidelines as well as the diagnostic differences and implications of the liquid-based Pap test and conventional Pap test will enable clinicians to determine the most appropriate test for a woman given the her clinical history, background, and risk factors. Active participation in informed clinical decision-making will help to ensure the best standard of care to women.

Since HPV is a viral infection, recurrence is a paramount issue for the provider to address with the patient.[74, 75] The complex relationship between oncogenic HPV persistence and the potential for progression toward cervical dysplasia and cervical cancer exacerbates the need for appropriate medical management and education related to oncogenic HPV and cervical cancer for women and clinicians.[74, 76-78]

Health care professionals who expand their care beyond the sole provision of disease knowledge help women manage oncogenic HPV infection in an empowering fashion. Improving a woman's understanding of her oncogenic HPV infection promotes self-care management and psychosocial coping. Oncogenic HPV-positive women need clinicians to be prepared for medical management challenges, as well as women's psychosocial and educational needs.[75, 79] Clinicians should provide information that is relevant and asked for by the patient, with attention to avoid the tendency to become too detailed. Clinicians should explain the details in appropriate language to avoid patient confusion and misunderstanding.[79], [80] Clinicians should provide educational messages that are more simple, appropriately repetitive, organized, and meaningful to their patients. [81, 82]

Clinicians need to highlight how oncogenic HPV transmission occurs, the difference between oncogenic HPV versus low risk or non-oncogenic HPV infection, viral remission versus persistent presentation, the risk of cervical dysplasia and cancer, pregnancy issues and how to establish a more balanced attitude between follow up and treatment of the disease.[75, 81] Patients should be provided with not only oncogenic HPV-specific information but also educational information on healthier habits in general.

A routine care plan for women diagnosed with oncogenic HPV, cervical dysplasia and cervical cancer should be developed by health care practitioners.[75] Recommended materials to include are: (1) having an initial crisis intervention plan after abnormal Pap test results; (2) being prepared to engage in supportive counseling to facilitate coping; and (3) having educational materials to promote optimal self-care, including adherence to a treatment and follow-up plan. Following diagnosis, clinicians should provide counseling to alleviate the patient's fears, anticipate and affirm feelings the patient may have, answer any questions, and advise the patient about follow-up. For many patients, a follow-up phone call or appointment within a few weeks post-diagnosis may be necessary to assess the patient's coping abilities, adherence to treatment, and understanding of persistent oncogenic HPV infection.

The significant time investment for the clinician may limit the scope of such a comprehensive approach. At a minimum, clinicians should become familiar with available resources in their area in order to provide referrals to support programs and other resources.[75, 83] Women with oncogenic HPV have noted that their clinicians do not advise and counsel them on emotional issues or ask about sexual practices.[75] Clinicians recognize this shortcoming, but less than half consistently counsel patients on these issues.[83] When women are diagnosed, the approach of most clinicians is to educate on the nature and transmission of HPV, practicing safer

sex, and disclosing diagnosis to their partners.[82, 84] Clinicians who promote a trusting relationship with women who have HPV are better prepared to talk to patients and encourage them to take active roles in their health care (i.e., empowering).[75, 79, 85]

EDUCATIONAL AND COUNSELING NEEDS OF WOMEN

Knowledge of HPV infection may affect a woman's emotional, sexual, and mental health in addition to her physical health.[75] Women who find out they have HPV infection are in need of effective and appropriate educational messages from the health care practitioner to better understand oncogenic HPV and its potential impact on their health. Research studies are underway as a result of the Congressional mandate to learn more about what women need and want to know about oncogenic HPV [86].

Educational materials should be used to reinforce verbal information provided by clinicians.[79] Combining written and oral information will not only provide reinforcement but also increase patient understanding and provide referent information post-visit. Clinicians providing written educational materials should review the materials with the patient rather than hand the materials to the patient at the end of the visit. This helps build a positive patient-provider relationship.

Psychosocial Effects of Abnormal Pap tests and HPV

In addition to the medical aspects of abnormal Pap tests and oncogenic HPV, women who are diagnosed with HPV face a disease that may impact their psychological and physical health.[87] Initial expectations of patients are focused on a "cure" for the disease and minimizing clinician visits.[79] Many times, women with HPV are unable to get sufficient information from their clinicians to understand oncogenic HPV and their specific situations[84] resulting in anxiety and uncertainty. Women's interpersonal relationships can become strained, which may further isolate the women from the problem.[84]

Shock is often the first reaction when a provider informs a woman that she has HPV.[75, 84] Research shows that the emotional impact of HPV is greatest at time of diagnosis.[75, 88] Many women feel their current partner may have been dishonest or infidel unfaithful causing greater emotional trauma.[75, 84, 89] As a result of the diagnosis, the woman may have negative feelings toward sexual intercourse and report subsequent sexual impairments.[75, 77, 81, 89] It has been reported that women express fears of being stereotyped and rejected, feel unclean or describe themselves in demeaning ways. Patients' recorded advice for others hearing a HPV diagnosis for the first time is to help them focus on ways to keep a positive outlook and maintain self-esteem.[87]

EMPOWERMENT AFTER HPV DIAGNOSIS

Empowerment is addressed as an intervention tool for clinicians to use with women who have HPV.[85, 90] Empowerment can be seen as promoting a healthy body image and sense of control; thus a responsibility to take care of her own body.[85] Feelings of empowerment and personal responsibility may lead to improved outcomes of adherence and treatment.[85] A sense of powerlessness can lead to feelings of being lost. Only the individual can empower

herself.[90] Therefore, the clinician's role is to support and facilitate this process by identifying obstacles to empowerment.[90] The process of empowerment is long-term and requires excellent rapport and communication between the clinician and woman.

Educational Resources for Clinicians and the Public

Existing educational resources for clinicians, patients, and health information seekers are often incomplete and remain difficult to keep current. The availability of culturally and linguistically appropriate oncogenic HPV and cervical cancer educational materials is limited. There is a desperate need to develop appropriate messages to assist with educational efforts. In the meantime, there are some sources of information that provide reasonably accurate and current information. Following is a list of specific resources for clinicians, patients, and health information seekers.

Resources for Clinicians

- American Cancer Society (www.cancer.org)
- American College of Obstetrics and Gynecology (http://www.acog.org)
- American Social Health Association (http://www.ashastd.org/hpv/hpv_overview.cfm)
- American Association of Reproductive Health Professionals http://www.arhp.org
- Centers for Disease Control and Prevention (http://www.cdc.gov/std/hpv)
- American Society for Colposcopy and Cervical Cancer Pathology (http://www.asccp.org)

Resources for Patients and Health Information Seekers

- American Social Health Association (http://www.ashastd.org/hpv/hpv_overview.cfm)
- Centers for Disease Control and Prevention (http://www.cdc.gov/std/hpv)

PROPHYLACTIC ANTI-HPV VACCINES AND CERVICAL CANCER

About twenty years elapsed between the first discovery of HPV viral particles in cervical specimens and the demonstration (by epidemiologic and molecular biology means) that oncogenic HPV types cause cervical cancer.[91] These studies found seven of the most prevalent oncogenic HPV types cause 87% of all cervical cancers. Vaccinations have historically been a cost-effective approach to prevent disease. Recent studies moving toward the development of the vaccine demonstrated that HPV proteins assemble spontaneously into virus-like particles (VLPs). These VLPs will cause an immune response that can protect individuals against new infection.[80, 92-96] The current HPV vaccine developments are still being conducted using the science of VLPs. An HPV vaccine could contribute to the reduction in invasive cervical cancer and its precursor lesions, prevention of other HPV-associated cancers in both males and females, and possibly, the elimination of genital warts that are HPV sequelae.

A few published results of early trials are available in the literature. One study demonstrated an immune response to oncogenic HPV16 VLPs protected vaccinated women from persistent oncogenic HPV16 infection.[92-95] A clinical trial using HPV16-HPV18 VLP showed high efficacy against both new and persistent HPV16 and HPV18 infections over 2-5 years.[80, 96] Use of a vaccine with two HPV strains is important since several stains of HPV are oncogenic and cervical adenocarcinoma resulting from persistent HPV18 infection is more difficult to detect by Pap test alone.

Based on the research summarized above, various types of prophylactic HPV vaccines are being developed for general use. Pharmaceutical companies are currently working with the Federal Drug Administration (FDA) for licensing. It is likely that an anti-HPV vaccine, targeting

four HPV strains including HPV16, HPV18, and as the common agents of genital and laryngeal warts, HPV6 and HPV11, will be available for general use in mid to late 2006.

HPV VACCINE CONSIDERATIONS

At a first glance, it might appear that HPV vaccination would forever solve the cervical cancer problem worldwide and that a vaccine would be the best approach to defeat this disease. However, strong caution must be used when evaluating the significance of these results, in the context of cervical cancer as a global public health issue.[97] Current vaccines in development have several considerations.

1. The combined vaccine for oncogenic HPV 16 & 18 will not protect against approximately 30% of infections.[98] There are several other oncogenic HPV strains that may cause cervical dysplasia and cancer.

2. Cervical cancer generally occurs among women who do not receive Pap test screening. If women are not receiving screening services due to barriers to care and other factors, enrollment of these same women into vaccination programs may also present challenges.[98] Missing women in vaccination programs will result in unchanged incidence and mortality rates.

3. The anti-HPV vaccines were found to be protective against persistent HPV infection and against cervical lesions caused by oncogenic HPV. It is most likely that, in time, this will translate into complete protection against cervical cancer, however, a direct demonstration that this is the case requires years of implementation, field study and follow-up.

4. Although initial results are quite encouraging, the duration of immunity to HPV after vaccination is not yet established. Therefore an optimal schedule of immunization is still being developed.

5. The anti-HPV16 and the anti-HPV16/18 vaccines were given to HPV-negative women. These specific vaccines may not alter the persistence of HPV infections among women who are already infected. Additionally, there is no information available on this vaccine's efficacy and safety in women who already have HPV infection by these oncogenic types. The HPV 16 and HPV 16/18 vaccines will also not protect against infection from other oncogenic types.

6. It is anticipated that the new HPV vaccine will be administered to young girls (at about 10 years of age, before the onset of sexual activity) and therefore the physician in charge of administering the vaccine will be a pediatrician, and not a gynecologist. If this is indeed the case, the choice of a vaccination age is still a matter of debate.[99] This poses the new need for pediatricians to be educated in sexually transmitted diseases, an area that they do not usually deal with in great depth.

7. The anti-HPV vaccine is probably the first of its kind against the sexually transmitted human papillomavirus. Therefore, its implementation requires careful planning and strategic administration along with public education similar to the experiences learned from the implementation of the Hepatitis B vaccine.

Cost Effectiveness (Prevention, Screening, Treatment)

With the advent of the Pap test, cervical cancer incidence and mortality rates have each declined more than 40% since 1973.[39] With the technology of the Pap test no women should develop cervical cancer nor die from it. The Pap test allows for early diagnosis of cervical dysplasia, which if managed appropriately will most likely result in the prevention of cancer and positive survival outcomes. Therefore the primary method to prevent cervical cancer is detection of cervical dysplasia and subsequent follow-up and treatment. The cost effectiveness of the Pap test and early treatment for cervical dysplasia obviously outweigh the negative outcomes: cancer development, cancer treatment costs, and unnecessary mortality from this preventable disease.

Advancements in screening technology (i.e. liquid-based Pap tests, HPV DNA testing, computerized re-screening) require the evaluation of current recommendations. However, institution of these new methods into recommendations should be based not only on the scientific results but on the cost-effectiveness in practice. The United States Preventive Services Task Force (USPSTF) evaluated the new cervical cancer screening technologies in the context of current screening recommendations in 2003.[100] Studies have shown that the liquid-based collection method has improved the sensitivity of the Pap test, especially among women with a low rate of cellular abnormalities. The USPSTF's findings imply the best use of HPV DNA testing with liquid-based testing could help identify women who should have yearly screenings versus women who may change screening routines to once every three years because of oncogenic HPV risk.[100]

Practical application of the HPV DNA test and the liquid-based Pap test in screening practices demonstrates a clear cost-effective model of care. In conventional Pap test methods,

abnormal cytology results, that is cervical dysplasia or inconclusive results of atypical squamous cells of undetermined significance (ASCUS), lead to a second office visit for follow-up. If a woman overcomes the additional monetary cost and inconvenience to adhere to a second visit, colposcopy is often recommended as the next step following an abnormal Pap test result. Research has shown the number of women who undergo colposcopy following a positive Pap tests incur additional cost. Use of the HPV DNA test using the cells from an initial liquid-based Pap test, as follow up to abnormal Pap test results can reduce these unnecessary second office visits and expensive procedures. HPV DNA testing as follow-up to women diagnosed with ASCUS is an especially effective management tool and has been modeled to show that HPV testing provided the same or improved life expectancy.[101]

The Centers for Disease Control and Prevention (CDC) recently published a report on survey results from clinicians with specialties that come into contact with sexually active patients. The survey assessed clinicians' knowledge, attitudes and practices related to HPV infection. A study results indicated nearly 90% offered Pap tests, 77% used liquid-based testing on occasion, and 54% used HPV DNA testing. Thirteen percent of the clinicians did not know about HPV DNA testing. Among the clinicians using the HPV DNA test, the specialty differed as well as many using the test for indications not currently approved by the Federal Drug Administration (FDA).

GAPS AND CHALLENGES IN CURRENT STRATEGIES FOR CERVICAL CANCER PREVENTION AND CONTROL IN SOUTH CAROLINA SCREENING PROGRAMS

Cervical Cancer Control Efforts in South Carolina

SCREENING PROGRAMS

The South Carolina Breast and Cervical Cancer Early Detection Program, known as the Best Chance Network (BCN), is a statewide program administered by DHEC and funded by the Centers for Disease Control and Prevention (CDC). The BCN provides free cervical and breast cancer screening and diagnostic services to underserved, income-eligible women between the ages of 47 and 64 throughout South Carolina. The BCN program currently works with healthcare providers who conduct cervical cancer screening using traditional conventional smear methods and liquid-based collection. However, liquid-based tests are currently being reimbursed at the Medicare-allowable conventional Pap test rate.

DHEC Family Planning offers one Pap test per year for women of reproductive age who are seeking methods for family planning. Costs for services are based on a sliding income scale and/or Medicaid eligibility. Women with no income and who are not eligible for Medicaid receive free screening services through program Title X federal money. Conventional Pap test methods are the only services provided. Follow-up services within DHEC Family Planning are not provided. Women needing follow-up and treatment are generally referred to private providers.

Palmetto Health's Certificate of Public Advantage (COPA), a hospital funded program to initiate community health outreach in the Midlands and Pickens County, has developed several

programs, including the Cancer Health Initiative. One component of Palmetto Health's COPA Cancer Health Initiative is to provide cervical cancer screenings to women ages 18 and above who are uninsured or underinsured and live in Richland, Lexington, Fairfield counties. Women who qualify receive annual Pap tests. If abnormal test results occur, women are notified by mail or phone and referred to a primary health care provider. Women without insurance and who have abnormal Pap test results receive free evaluative services though the COPA Cancer Health Initiative. Notifications of paid follow-up services are delivered to the woman when she receives a follow-up appointment. The Cancer Health Initiative makes financial arrangements with the follow-up physician to ensure the patient is not billed at time of follow up.

Additional limited resources are available to assist women to receive Pap test screenings. State, local and regional medical centers in collaboration with universities and private foundations offer screening programs for eligible women.

TREATMENT

With the passage of the Breast & Cervical Cancer Treatment Act in 2000, South Carolina has been able to provide treatment for cervical cancer diagnoses and related cervical dysplasia to the Best Chance Network participants. Since 2001, South Carolina has offered treatment coverage under Medicaid through an agreement with the Department of Health and Human Services. The availability of treatment for the Best Chance Network was a significant milestone as PL 101-354 only authorized funds for screening and diagnostic services for breast and cervical cancer. Effective July 1, 2005, increased state funding for the Breast and Cervical Cancer Program at DHHS enabled expansion of this Medicaid coverage by providing increased matching dollars for appropriated federal funding. Women not screened through BCN and under

the age of 65 who meet income and insurance guidelines are eligible to apply for Medicaid through this program.

SURVEILLANCE

Surveillance of cervical cancer is conducted by the award-winning South Carolina Central Cancer Registry at DHEC. Established in 1993, the SCCCR provides statewide cancer incidence rates for cervical cancer and all other cancers occurring among South Carolinians. Newly diagnosed invasive cervical cancer cases are reported from hospitals, pathology labs, freestanding treatment centers, and physician offices. The SCCCR data has received gold certification for completeness, timeliness, and quality by the North American Association of Central Cancer Registries.

This statewide cancer surveillance system provides invaluable information for cervical cancer control in South Carolina. SCCCR data uses include: descriptive reports of the occurrence of cervical cancer in SC (i.e. number of new cases and deaths, cellular types of cervical cancer, and severity/stage of new cervical cancer cases at time of diagnosis); trends in the occurrence of cervical cancer as well as deaths due to the disease; identification of high risk groups to be targeted for education, prevention, and screening; evaluation of cervical cancer control programs; investigation of the possible occurrence of more cervical cancer cases than normal from a geopolitical area; and information for epidemiologic and medical research on cervical cancer in South Carolina.

Gaps and Challenges

SCREENING PROGRAMS

The BCN Program can only screen and provide diagnostic services for a defined sub-group of the population in South Carolina. The BCN eligibility criteria are restricted by income and age due to level federal funding and established program guidelines. Younger women who do not meet the income guidelines are also at risk of not being screened and followed up. Furthermore, liquid-based testing is currently approved for enrolled women in the program. However the reduced federal reimbursement for liquid-based testing services discourages laboratories to provide these services to health care providers participating in the BCN program. Consequently, certain women in the BCN program will not receive the benefit of this improved screening technology as others in the program and those beyond the program until reimbursement of liquid-based tests occurs at the higher allowable Medicare rate and not at the conventional Pap test rate.

DHEC Family Planning services are restricted to serving women in the reproductive age range who are seeking a method of birth control. DHEC does not have a cancer screening program for women who do not meet the criteria of BCN or are not seeking family planning services. Follow-up for abnormal Pap tests found among family planning patients is not provided. DHEC does not have the capacity or resources to provide follow up care. Therefore referral of these patients to private providers may often result in non-adherence. Introduction of liquid-based Pap tests would improve screening services. The insufficient number of nurses in DHEC Family Planning also inhibits the ability to serve.

Palmetto Health's COPA Cancer Health Initiative Program for cervical cancer screening experiences financial limitations as well as being geographically-limited to women who live in the Midlands (Richland, Lexington, and Fairfield counties).

SURVEILLANCE

Since severe cervical dysplasia indicates the possibility of progressing to invasive cervical cancer, surveillance of this condition is important. Measuring the distribution of the occurrence of severe cervical dysplasia is not currently conducted by CDC-funded registries. Also, a state match requirement of 25% of the total budget is required to maintain federal funds for cancer surveillance. As the registry matures and federal budgets increase, maintaining an adequate state-funded match becomes difficult.

SOUTH CAROLINA PARTNERSHIPS FOR CERVICAL CANCER PREVENTION AND CONTROL

Partners

SOUTH CAROLINA CANCER ALLIANCE

The South Carolina Cancer Alliance (SCCA), a statewide partnership between grassroots stakeholders and professionals interested in reducing the impact of cancer in SC, is finalizing a state plan for cancer control. Cervical cancer is a priority in the state cancer plan. The Prevention and Early Detection Task Forces developed objectives to increase cervical cancer screening and follow-up among at risk women. DHEC's Division of Cancer Prevention and Control, partner to the SCCA, was integrally involved in the development of the state cancer plan, providing oversight and management of the process. Public release of the plan is expected in Fall 2005.

DHEC CANCER CONTROL ADVISORY COMMITTEE

The DHEC Cancer Control Advisory Committee (CCAC), established by SC Code Section 44-35-90, advises DHEC on professional issues pertaining to cancer prevention, detection, care and surveillance. The CCAC assists DHEC in maintaining relationships with community and other healthcare providers.

State legislative recommendations for cervical cancer control should be coordinated through the CCAC. Coordination could include the establishment of a Cervical Cancer Task Force under the purview of the CCAC in alignment with their legislative mandate.

DEPARTMENT OF HEALTH & HUMAN SERVICES – SC MEDICAID

On July 1, 2005, one million dollars in state funds were earmarked for cervical and breast cancer treatment under the Breast & Cervical Cancer Treatment Act. The Department of Health and Human Services (DHHS) in partnership with DHEC and community advocates worked successfully to attain these treatment funds. These funds allow expansion of cancer treatment to women who are diagnosed outside the Best Chance Network. With this new funding, women will be eligible to receive treatment for cervical dysplasia (CIN II, III) and invasive cervical cancer. These women will qualify for Medicaid to cover their treatment if they are younger than 65 years of age; do not have insurance coverage that covers treatment of precancerous lesions and 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 this treatment.

RESEARCH IN SOUTH CAROLINA (1993 – PRESENT)

Peer-Reviewed Published Literature

The very first study of the relationship between oncogenic HPV infection and Cervical Intraepithelial Neoplasia (CIN) in South Carolina was performed by Ann L. Coker, in collaboration with Lucia Pirisi's group, and published in Cancer Epidemiology, Biomarkers and Prevention in 1993.[102] In this study, all cases of CIN II or III (n = 28), CIN I (n = 114) and atypia (n=115) were identified, together with 223 controls with normal cervical cytology, among a cohort of approximately 6000 cervical samples collected from March through December 1991. The study observed an increase in the prevalence of oncogenic HPV types 16, 18, and 33 with increasing severity of cervical lesions, which was highly significant (P = 0.0001). This work confirmed what was rapidly becoming evident in other populations: a strong association of oncogenic HPV types with cervical dysplasia lesions, particularly among White women.

The same research team followed up with various studies, including a nested case-control study of oncogenic HPV infection and CIN[103], including only women who had normal cervical cytology (N = 2905) at baseline and provided a cervical sample for HPV typing at the first visit, and had subsequent follow-up visits for up to five years at family planning clinics. This study too showed that having an oncogenic HPV type at baseline was associated with a marked increase in risk for cervical lesions. The association between oncogenic HPV positivity and squamous intraepithelial lesions (SIL) development was strongest in the first year of follow-up and declined in the five years of follow up. This observation was explained by more recent studies by this and other groups, clearly demonstrating that oncogenic HPV infection can be

transient (in most cases) or persistent (in a minority of the cases), and that persistence is a much stronger risk factor for cervical dysplasia than transient infection.

Coker and collaborators also conducted a study of the influence of hormonal (oral, injectable, or levonorgestrel [Norplant, Wyeth-Ayerst, Philadelphia, PA]) and barrier methods of contraception on the risk of cervical squamous intraepithelial lesions (SIL), while adjusting for oncogenic HPV infection. This study, conducted on 823 women who attended state health department family planning clinics from 1995 to 1998, found no increased risk of CIN in users of oral or injectable contraceptives. However, and most importantly for the prevention of cervical dysplasia oncogenic in HPV-positive women, barrier method use of longer duration was associated with a reduced risk of SIL among women who were positive for oncogenic HPV. This result indicated that while barrier methods of contraception may not provide complete protection against HPV infection, they still have the potential of decreasing the risk of developing cervical dysplasia, and as such has important clinical and public health implications.

Other publications by Coker and her collaborators address the associations between smoking (active and passive) and cervical dysplasia [104], important associations between intimate partner violence and the risk of cervical cancer [105], as well as a relationship between psychosocial stress and cervical cancer risk.[106]

Predictors for participation in Pap test screening in a socio-economically disadvantaged older population were studied in a population including very low income (< $10,000) and older women (65 and over).[107] This study found that lack of access to a phone was a strong predictor for nonparticipation in cervical cancer screening. Also, a low income and factors such as being widowed and not having a family history of cancer were also associated with a lack of participation in cancer screening.

A study funded by the Healthy South Carolina Initiative in 1998 examined participation in a free follow-up program among rural women in SC DHEC family planning clinics having a minor abnormality in their annual Pap report. The program was designed to provide colposcopy, evaluate and treat women for vaginitis and sexually transmitted infections, follow-up on Pap tests for two years and treat women with cervical dysplasia when identified on biopsy. The study enrolled 316 women. Both formal and informal strategies were used to maintain participation in follow-up. Despite delivery of onsite services and free care, completion rates were low implying that many women suffer indirect costs associated with obtaining care. This is especially important for women whose jobs pay by the time worked and provide no health benefits or paid time off [108]

Unpublished Research

SC researchers in South Carolina have also conducted unpublished research studies. Special Interest Projects (SIPs) funded by the CDC have addressed follow-up and adherence among women with abnormal Pap tests results. These qualitative studies have explored the factors surrounding the completion of timely follow-up and considered clinician as well as patient factors. The populations investigated were all low-income and uninsured populations in South Carolina.

Researchers for this study examined how closely the factors identified by women related to the factors that clinicians believed affect their clients' ability to follow-up. Results revealed that clinicians' perceptions of women's lack of adherence to follow-up were congruent with women's reasons for not completing follow-up: competing life priorities, financial and transportation challenges, and co-morbid health conditions. However, while clinicians perceived that fear and lack of understanding were major barriers, the women indicated that neither interfered with seeking care. Women also noted that clinicians' sensitivity and concern, staff's friendliness, assistance with scheduling and reminders about follow-up appointments were key facilitators.

Another study from the same CDC-funded SIP addressed the role of competing life priorities on follow-up adherence. Findings revealed that meeting the needs of significant others, living on restricted income, and living with co-morbid conditions contributed toward their ability to obtain the prescribed follow-up.

Additional independent qualitative research explored the patient-provider relationship from the women's perspective to understand adherence behavior for abnormal Pap tests. Results

clearly indicated that the low-income, uninsured women did not comprehend the implications of having an abnormal test result. While the women used medical terminology to describe their results and the tests they underwent, they merely adopted the usage of those terms without understanding the information that was being communicated to them by their physicians. Low literacy levels were very evident among this study sample that was clearly motivated and sought out care to take charge of their health.

An epidemiologic study was conducted to investigate whether low-income women are at increased risk of dying from cervical cancer due to late stage diagnosis and sub-optimal treatment. South Carolina Central Cancer Registry data were used to address these associations. Study results showed stage of cancer at diagnosis was a strong predictor of survival, plus an effect modifier for the association between poverty and survival. Women diagnosed with early stage cervical cancer, residing in regions of high poverty were significantly more likely to die. This finding may indicate poor women even though diagnosed early with cancer, may be disadvantaged in receiving treatment, resulting in increased mortality. The study also demonstrated poverty was associated with sub optimal treatment by stage at diagnosis and those receiving sub-optimal care were twice as likely to die.

There may be other unpublished cervical cancer research studies, previous and on going, performed by SC researchers using SC data. This brief description of the research conducted in South Carolina around cervical cancer prevention and control is limited to what was made available through the participants in this report.

Recommendations

1. Institute liquid-based Pap testing among DHEC Family Planning Clinics according to the findings of current assessments regarding the feasibility of instituting liquid-based testing in these clinical settings. The liquid-based test will increase the number of true positives thereby improving the ability to identify new cases (incidence) and prevent deaths (mortality).

    a. IMPACT to DHEC: Use of liquid-based testing in family planning clinics may result in an increased cost per test but DHEC will realize an increased cost-benefit through fewer repeat exams, a reduction in total workload for annual exams and early detection that may reduce total medical and public health costs. Screening women with the liquid-based Pap test will identify women who may need a Pap only once every three years versus every year.

    b. IMPACT to SC: South Carolina is one of two states in United States Public Health Service Region 4 still using conventional Pap tests in state supported local health department family planning clinics for cervical cancer screening. If instituted, DHEC practices would come more in line with what is becoming the standard of care.

2. Institute FDA-approved HPV DNA testing among DHEC Family Planning Clinics as the standard of care.

a. IMPACT to DHEC: Use of FDA-approved HPV DNA testing in DHEC Family Planning Clinics will reduce the number of referrals for follow-up colposcopy and testing to outside providers due to the improved assessment for immediate follow up for oncogenic HPV types with abnormal Pap tests.

b. IMPACT to SC: Detecting and identifying cervical dysplasia and cancer early will identify more women with this disease.

c. IMPACT to SC: Reduced healthcare costs to private providers due to full reimbursement of HPV testing among indigent women.

d. IMPACT to SC: Decrease psychosocial burden among South Carolina women by reducing additional, possible unnecessary follow up through HPV test utilization.

3. Initiate state funding to develop and enhance cervical cancer screening programs for women who are not eligible for screening through current programs due to lack of program capacity or federal program eligibility criteria.

   a. IMPACT to DHEC: Significant increase in staff to manage new cancer screening program for this new group of eligible women

   b. IMPACT to DHEC: Data systems modification to collect and monitor women receiving services.

c. IMPACT to SC: A targeted cancer screening program for indigent women who do not currently qualify for existing screening mechanisms will continue to reduce cervical cancer incidence and mortality in the state.

d. IMPACT to SC: Women participating in SC Breast and Cervical Cancer Early Detection Program will need to receive the same level of care as women screened through a state funded cervical cancer screening program. Current federal program restrictions on reimbursement for liquid-based Pap test reimbursement discourage laboratory participation and physician's incapability to administer this improved Pap test method.

4. Improve state surveillance and research funding to investigate the complex barriers to care faced by SC women in access to screening programs and support for follow-up care procedures and treatment of severe cervical dysplasia or cancer.

   a. IMPACT to DHEC: Foster collaborative research and implementation of community-based programs through South Carolina Cancer Alliance task forces.

   b. IMPACT to SC: Enhance community-based and university assisted research initiatives to measure characteristics unique to the South Carolina population.

5. Explore existing partnerships to educate health care professionals and women utilizing research-based materials and prevention technologies on HPV and cervical cancer.

a. IMPACT to DHEC: Identify state funds to facilitate education of South Carolina women on HPV and cervical cancer.

b. IMPACT to SC: Improve understanding and awareness of HPV to reduce cervical cancer incidence and mortality in South Carolina.

c. IMPACT TO SC: Increase awareness of and participation in community-based participatory research efforts to develop culturally relevant and appropriate messages enabling engaging targeted audience members as well as professionals and entities involved in education and dissemination need to occur. Participants will involve public health practitioners, health educators, researchers at schools of public health, historically black colleges and universities, other academic institutions, state and local health departments as well as local citizens, and key leaders representing the different priority communities of interest.

Closing Statement

No women should be diagnosed or die from cervical cancer. Since the introduction of the Pap test, cervical cancer incidence and mortality rates have dropped dramatically among all women; however Black women and women of low socioeconomic status continue to feel a heavier burden related to cervical cancer deaths.

Conventional Pap test methods as the current standard of cervical cancer screening in South Carolina, is a sufficient screening procedure for women who have normal routine Pap test results. However, among indigent or low-income women who infrequently access healthcare services, the implementation of liquid-based Pap testing and HPV DNA testing is imperative because true positives for cervical cancer may be missed. Therefore, implementation of these advanced screening procedures at initial visits will help distinguish women with oncogenic HPV and mild/severe cervical dysplasia who need immediate and necessary follow-up for abnormal results otherwise they may develop into cervical cancer (true positives). In addition, liquid-based testing at initial screening will decrease the number of women who do not adhere to second office visits for definitive diagnosis and follow-up. Adherence to follow up care and diagnosis of cervical dysplasia and or early stage cervical cancer is the only way to prevent cervical cancer mortality at this time. SC must ensure all women with abnormal cellular changes are screened and identified (true positives). SC must use the newest effective technologies to reduce the state's high cervical cancer incidence and mortality rates.

HPV vaccines are in development. However, when approved for initiation into vaccine programs for children and adolescents, the prevention of oncogenic HPV infection by vaccine is only one step to cervical cancer prevention. Vaccines in development have limitations.

Currently, the vaccines in design and testing are limited to two of the most common oncogenic types in the United States. Therefore oncogenic HPV infection will continue to occur among the types not present in the vaccine. It will be necessary to continue Pap test screening and HPV DNA testing for many years after the implementation of HPV vaccination programs in the general population to monitor the vaccination effectiveness.

Federal funds, the CDC-funded SC Breast and Cervical Cancer Early Detection Program and Title X money for Family Planning services, in conjunction with private money though hospitals and universities, currently support cervical cancer screening among qualifying low-income or indigent South Carolina women. The state must help take care of South Carolina women who are ineligible for current programs and need cervical cancer prevention, detection and treatment.

State legislative recommendations for cervical cancer control should be coordinated through the DHEC Cancer Control Advisory Committee (CCAC). Coordination could include the establishment of a Cervical Cancer Task Force under the purview of the CCAC in alignment with their legislative mandate.

The recommendations of this report are based on current scientific evidence supporting new technologies to prevent cervical cancer along with the considerations of the unique characteristics of the South Carolina population. Published and unpublished epidemiologic, health services and health education studies by local researchers also support the recommendations presented. Research on the items discussed in this report is ongoing. Continued review of new evidence-based literature is important to gain continued support of these recommendations.

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Appendix A: Legislative Proviso

STATUTES AT LARGE
General and Permanent Laws—2004
Section 9 – J04 – DEPARTMENT OF HEALTH AND ENVIRONMENTAL CONTROL

9.50. (DHEC: Cervical Cancer Study) The department is directed to study strategies and new technologies that are effective in preventing and controlling cervical cancer. Because of the proven cost effectiveness of vaccines this method of prevention should be one of the areas of focus of the study. In developing the study the DHEC Commissioner shall consult with groups and/or institutions with expertise in the prevention and treatment of cervical cancer. The groups selected to provide consultation shall be at the discretion of the Commissioner. The findings of the study shall be provided in a report to the Chairman of the Senate Medical Affairs Committee and the Chairman of the House Medical, Military, Public Affairs Committee no later than June 15, 2005.

9.48. (DHEC: Cervical Cancer Study) The department is directed to study strategies and new technologies that are effective in preventing and controlling cervical cancer. Because of the proven cost effectiveness of vaccines this method of prevention should be one of the areas of focus of the study. In developing the study the DHEC Commissioner shall consult with groups and/or institutions with expertise in the prevention and treatment of cervical cancer. The groups selected to provide consultation shall be at the discretion of the Commissioner. The findings of the study shall be provided in a report to the Chairman of the Senate Medical Affairs Committee and the Chairman of the House Medical, Military, Public Affairs Committee no later than October 14, 2005.

Appendix B: Cervical Cancer Brochure

UPCOMING EVENTS

March 31, 2005
Dr. Alan Shaw, Merck scientist visits SC

April 29, 2005
SC Cancer Alliance Annual Meeting

May 2005 (TBA)
SC Cervical Cancer Symposium

For information on cervical cancer activities at DHEC contact:

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Irene Prabhu Das, MPH, Director
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prabhudi@dhec.sc.gov

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Cervical Cancer Prevention: An Issue for South Carolina's Women

Proviso 9.50 — Achievements

SC Cervical Cancer Facts

Women in Government's Report: Update from South Carolina

Upcoming Cervical Cancer Events in South Carolina

D H E C
PROMOTE PROTECT PROSPER

SC Department of Health and Environmental Control

2004 Legislative Session Proviso 9.50

(DHEC: Cervical Cancer Study)

The department is directed to study strategies and new technologies that are effective in preventing and controlling cervical cancer. Because of the proven cost effectiveness of vaccines this method of prevention should be one of the areas of focus of the study. In developing the study the DHEC Commissioner shall consult with groups and/or institutions with expertise in the prevention and treatment of cervical cancer. The groups selected to provide consultation shall be at the discretion of the Commissioner. The findings of the study shall be provided in a report to the Chairman of the Senate Medical Affairs Committee and the Chairman of the House Medical, Military, Public Affairs Committee no later than June 15, 2005.

Proviso 9.50 — Achievements

September 2004:

- SC expert core study group meets
- Outline of report developed

September/October 2004:

- Parallel consultant group to core study team developed

November 2004:

- *Status of Cervical Cancer Prevention and Control* : 1st Draft

January 2005

- Revisions for report

January-March 2005

- Revisions for report

STATEWIDE OBJECTIVES FOR CERVICAL CANCER PREVENTION*

- "Support dissemination of new information to provide the public with current and evolving science, technology, and guidelines specific to cervical cancer screening."
- "Increase the proportion of women who receive pap smears, appropriate referral and follow-up."

* Strategies from DHEC Comprehensive Cancer Plan and Health Services Operational Plan

SC Cervical Cancer Facts

Pap test Screening[1]: Among women surveyed, 86.4% received a Pap test within the last 3 yrs.

Incidence[2]: In 2001, 205 cervical cancer cases were diagnosed in SC.

Cervical cancer incidence rates are 1.5 times higher among Black women compared to White women.

White women are more often diagnosed with early stage cervical cancer than Black women.

Mortality[2]: SC ranks 8th in the nation for cervical cancer mortality.

Cervical cancer mortality rates are decreasing for both White and Black women; however a disparity exists by race.

Cervical cancer deaths rates for Blacks are nearly 3.5 times higher than for Whites.

SC Cancer Alliance
Cancer Report Card, 2004

A South Carolina woman's risk of getting cervical cancer is similar to the rest of the nation earning SC a grade of 'C', however, the risk of dying from the disease is far greater (SC grade for cervical cancer deaths='F').

www.sccanceralliance.org

[1] SC BRFSS 2002
[2] SC Central Cancer Registry (2004 finalmasterfile)

Women in Government

A Call to Action: The State of Cervical Cancer Prevention in America [3]

South Carolina's Update

Data Collection and Tracking:

DHEC's SC Central Cancer Registry (SCCCR) is an incidence-based cancer surveillance system that collects all cancers diagnosed since 1/1/1996 thru present.

www.scdhec.net/co/phsis/biostatistics/SCCCR/SCCCRmain.htm

DHEC's Best Chance Network (BCN) Program provides Pap tests and diagnostic services for cervical cancer among women who qualify by age, income and insurance criteria.

www.scdhec.gov/health/chcdp/cancer/bcn.htm

DHEC's Behavioral Risk Factor Surveillance System (BRFSS) conducts telephone surveys to assess Pap test use among SC women.

www.scdhec.gov/hs/epidata/brfss_index.htm

DHEC offers Family Planning Services for women of any age and criteria.

www.scdhec.gov/health/mch/wcs/fp/index.htm

[3] Published by Women In Government.
http://www.womeningovernment.org/

Appendix C: Screening Recommendations for Cervical Cancer

(Adapted from Smith, R.A & Zoorob, R.)

Medical organization	Screening recommendations
AAFP	Pap test at least every 3 years to women who have ever had sexual intercourse and who have a cervix
ACOG	Annual Pap test and pelvic examination beginning at age 18 or when sexually active; after 3 or more tests with normal results, Pap test may be performed less frequently on physician's advice
ACS*	▪ Begin cervical cancer screening about 3 years after onset of sexual activity and by age 21; annual screening with regular Pap test or every 2 years using the liquid-based cytology ▪ At age 30, women with 3 normal Pap test results in a row may get screened every 2 to 3 years with regular or liquid-based testing; women who have certain risk factors should continue to be screened annually ▪ An option for women over 30 is to get screened every 3 years with either conventional or liquid-based testing, plus HPV DNA testing ▪ Women 70 years or older with 3 or more normal Pap tests in a row and no abnormal Pap test results in past 10 years may choose to stop having cervical cancer screening
AGS	Pap test every 3 years until age 70; in women of any age who have never had a Pap test, screening with at least 2 negative smears, 1 year apart
AMA	Annual Pap tests and pelvic examination starting at age 18 (or when sexually active); after 3 or more normal annual Pap tests, the Pap may be performed less frequently at the physician's discretion
CTFPHC	Pap test annually beginning at age 18 or following initiation of sexual activity; after 2 normal results, perform Pap tests every 3 years to age 69
USPSTF	Pap test at least every 3 years in women who have ever had sexual intercourse and who have a cervix; discontinue regular testing after age 65 if Pap test results have been consistently normal

*In 2003, the American Cancer Society updated their screening recommendations for cervical cancer.
Abbreviations for medical organizations: AAFP = American Academy of Family Physicians; ACOG = American College of Obstetricians and Gynecologists; ACS = American Cancer Society; AGS = American Geriatrics Society; AMA = American Medical Association; CTFPHC = Canadian Task Force on Preventive Health Care; USPSTF = United States Preventive Services Task Force

Figure 1A
1996-2001 SC Cancer Incidence Among Blacks Compared to 2001 US Incidence, Invasive Cervical Cancer

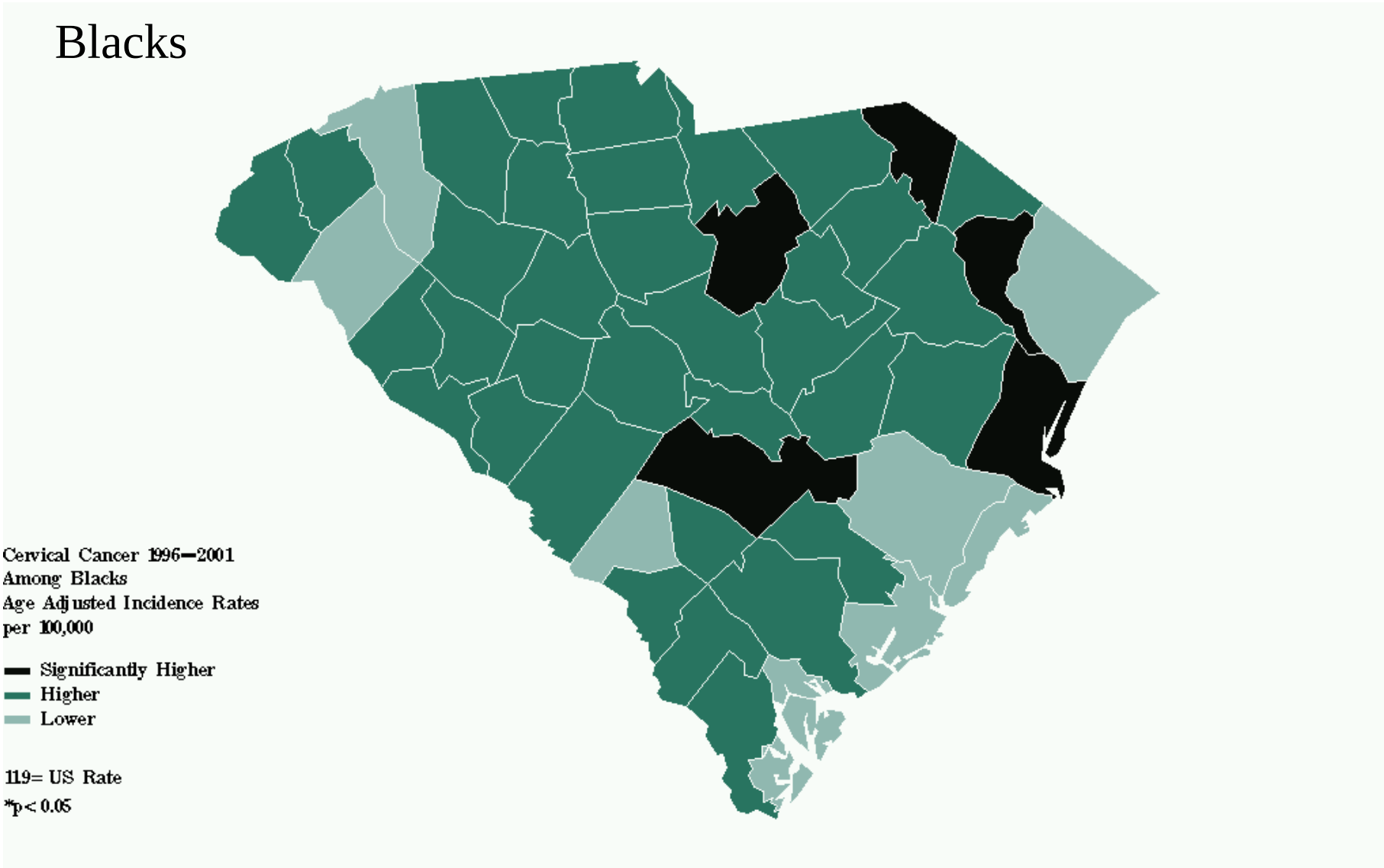

Figure 1B
1996-2001 SC Cancer Incidence Among Whites Compared to 2001 US Incidence
Invasive Cervical Cancer

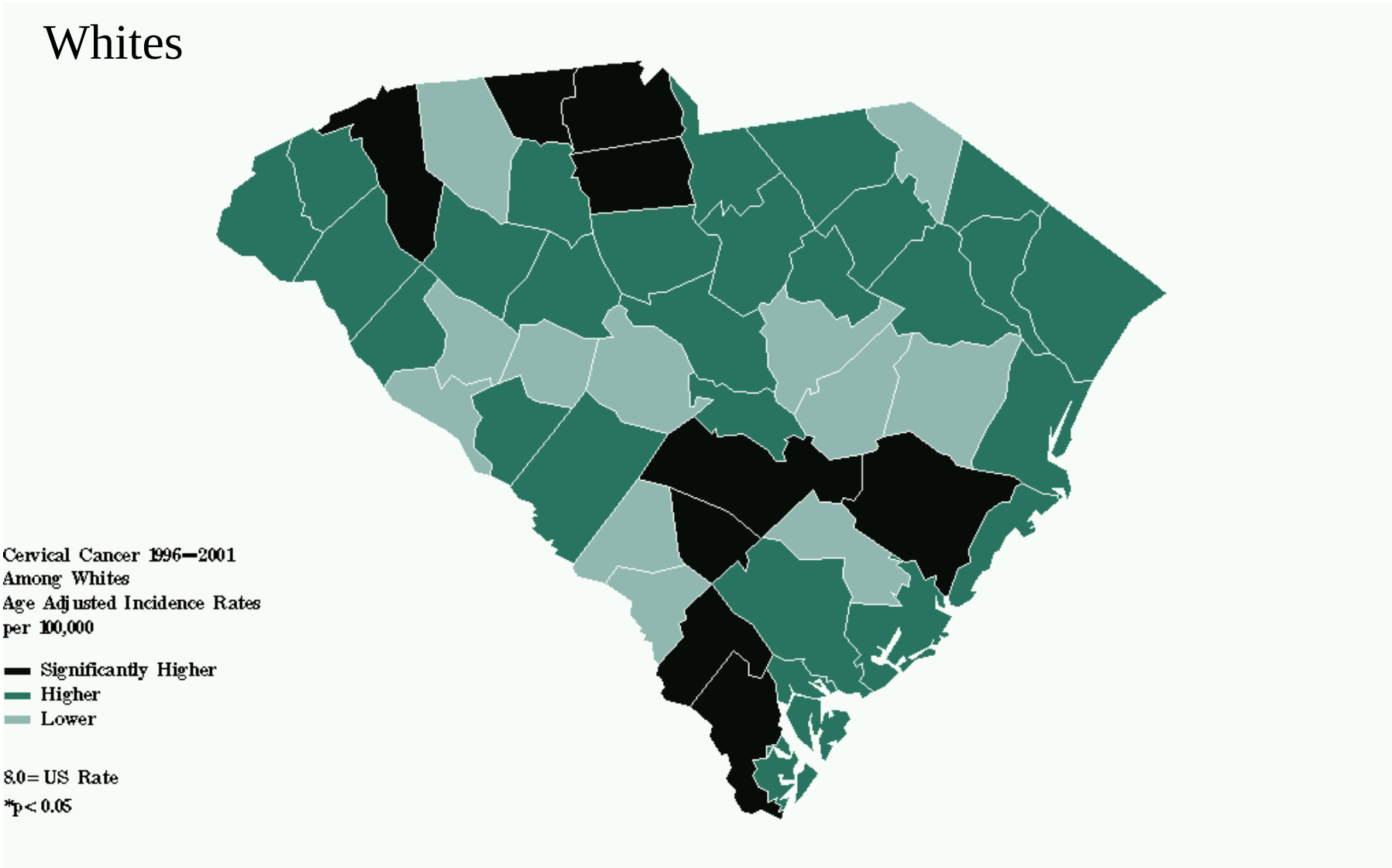

Figure 2
1996-2001 South Carolina Cervical Cancer Incidence by Age Group

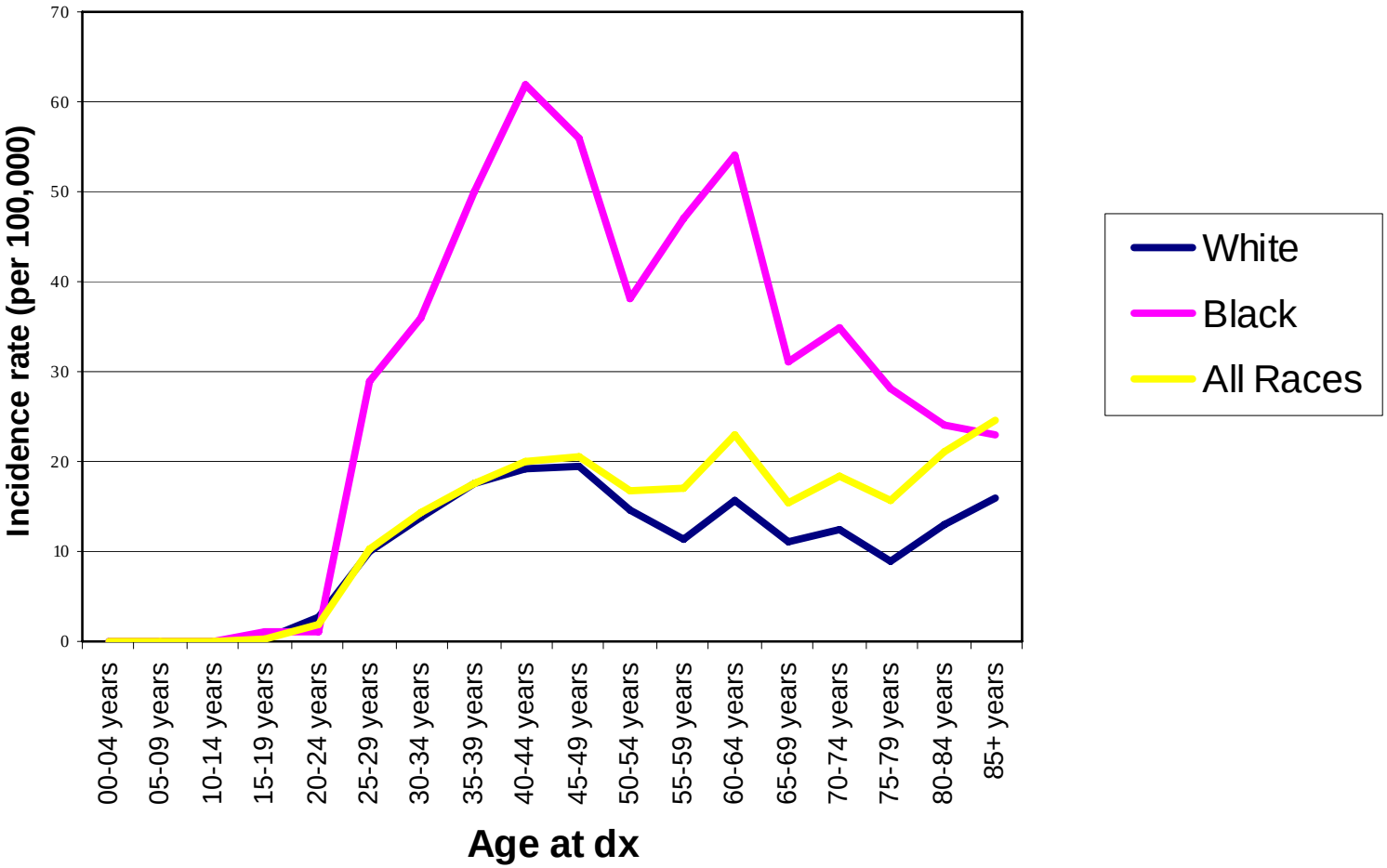

Figure 3A
1996-2001 Invasive Cervical Cancer Incidence By Stage at Diagnosis
Black Women

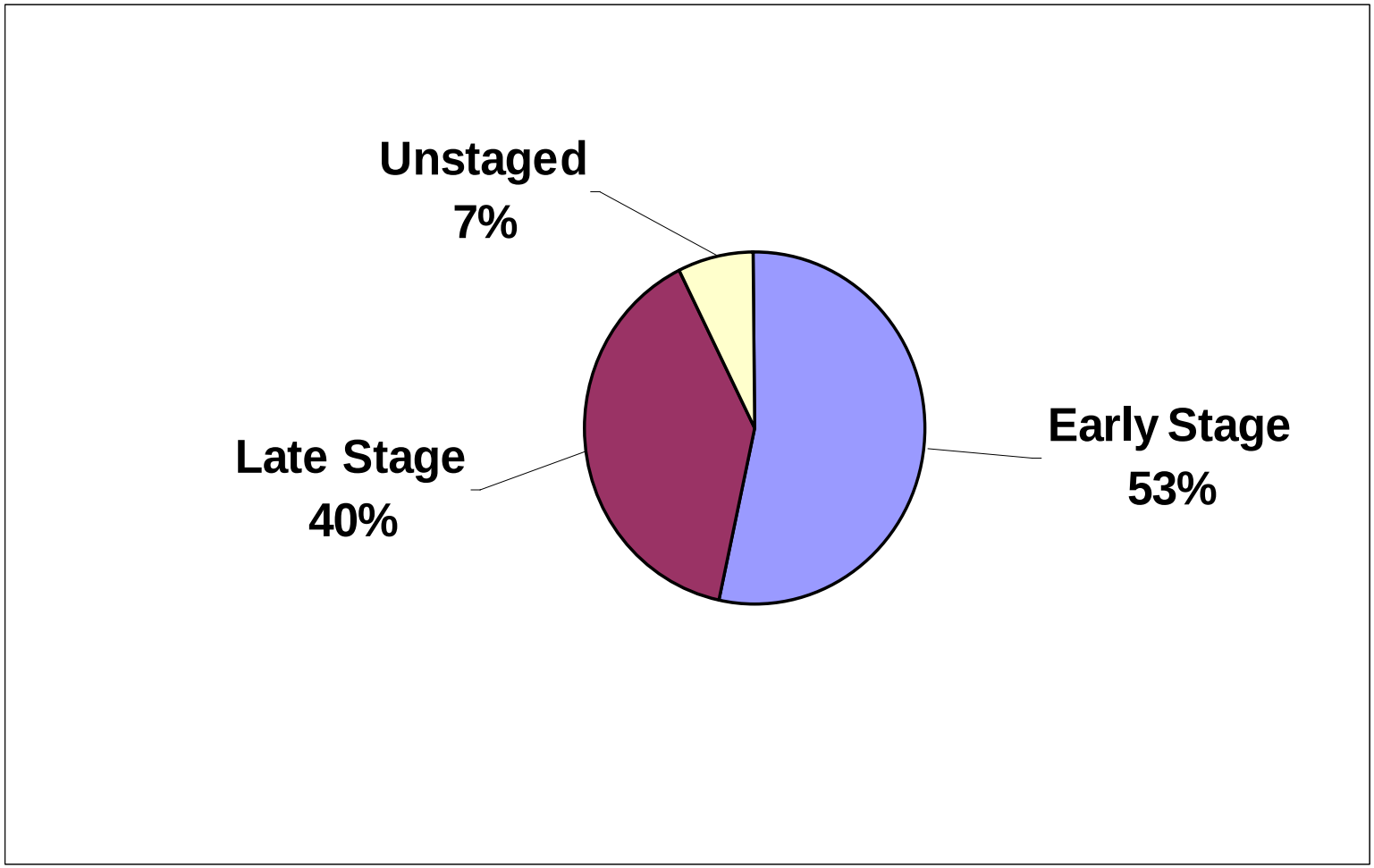

Figure 3B
1996-2001 Cervical Cancer Incidence By Stage at Diagnosis
White Women

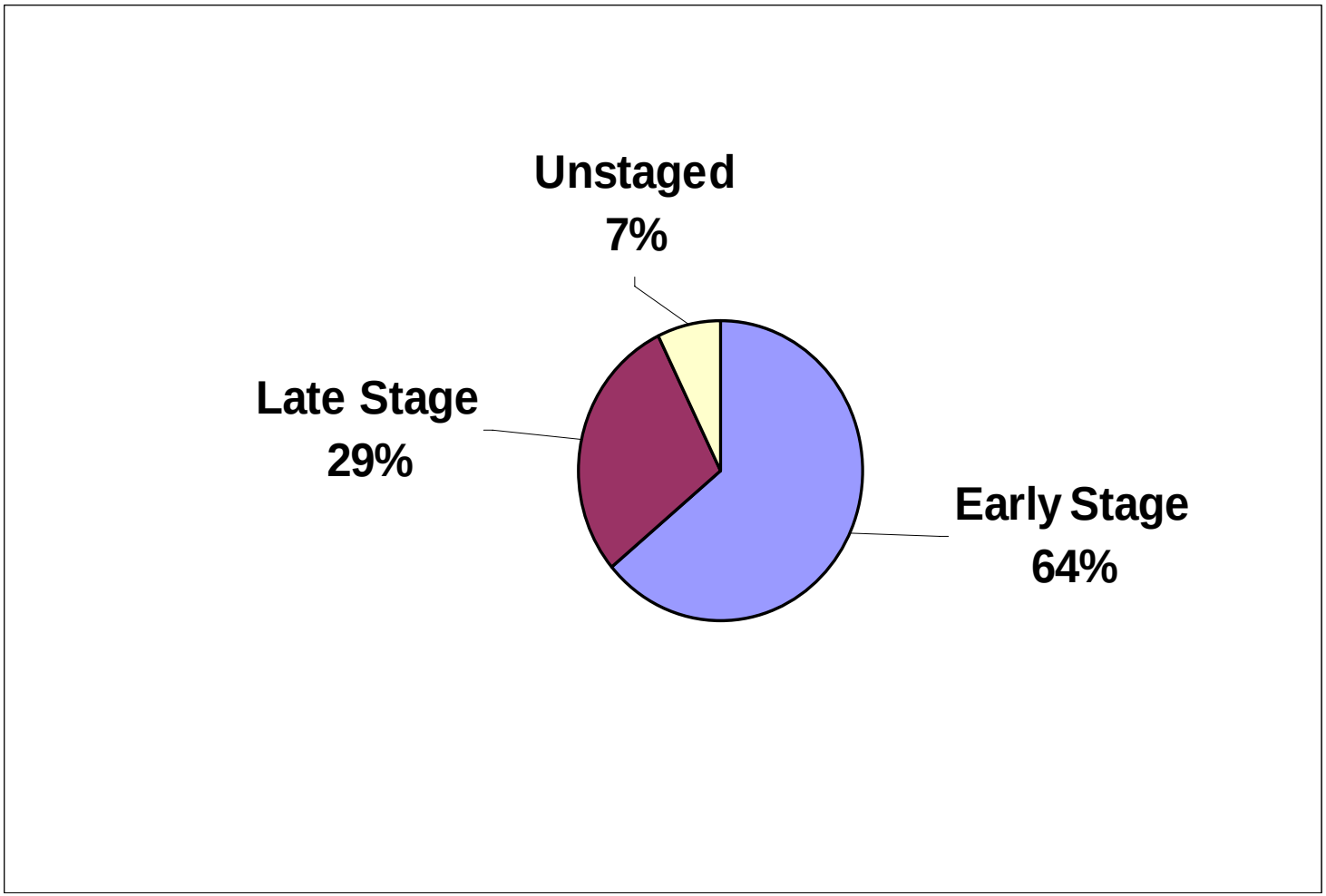

Figure 4A
1996-2001 SC Cancer Mortality Among Blacks Compared to 2001 US Mortality
Invasive Cervical Cancer

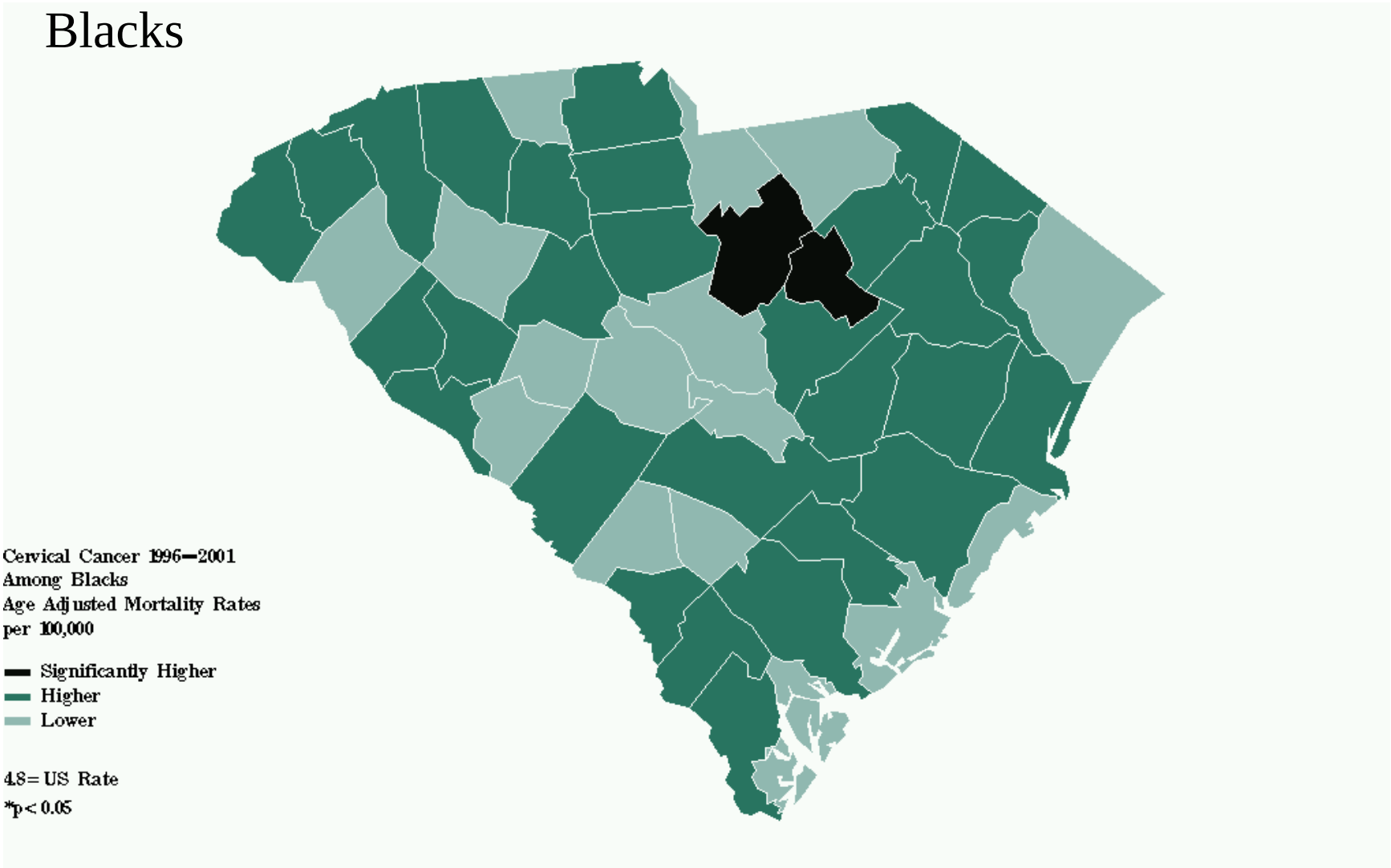

Figure 4B
1996-2001 SC Cancer Mortality Among Whites Compared to 2001 US Mortality
Invasive Cervical Cancer

Whites