Cervical Cancer: Disparities in Screening, Treatment, and Survival

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Introduction
This article will use a case study to review the literature on cervical cancer disparities by race, ethnicity, and socioeconomic status. The patient exemplifies several issues facing underserved populations, including the presence of comorbid diseases, failure to have follow-up visits for colposcopic evaluation and treatment of abnormal Pap smears, and ultimate presentation with invasive cervical cancer. She is unable to keep appointments, receives suboptimal treatment, and is unlikely to be cured of her disease.

Case Study. S. R. is a 41-year-old African-American female with a history of schizophrenia. The patient also has a history of abnormal Pap smears and has failed to appear for colposcopy on multiple occasions. Despite many attempts, her medical care providers have been unable to reach the patient, and she ultimately presents to the emergency ward with profuse vaginal bleeding and a hematocrit of 9% (normal: 36–48%). A pelvic examination reveals a large bleeding cervical mass. Emergency biopsy result is consistent with invasive squamous cervical cancer. The patient undergoes emergency radiation treatment and receives multiple blood transfusions. Social Services becomes involved in her care, and she is eventually discharged home in stable condition with a detailed plan for radiation therapy and sensitizing chemotherapy. She completes her radiation treatment after several interruptions but receives less than half of the recommended chemotherapy regimen because of missed appointments.

Cervical cancer is now a preventable disease and any woman presenting with invasive cervical cancer should be viewed as a failure of screening. The developing world accounts for ~80% of incident cervical cancers, and the disproportionate number of cervical cancer patients can largely be attributed to the lack of organized Pap smear screening programs (1, 2). Despite abundant healthcare resources in the United States, women in minority, socioeconomically disadvantaged, and rural populations have not equally benefited from Pap smear screening (3).

HPV\(^2\) Infection and Cervical Neoplasia. HPV has been implicated in the development of virtually all cervical cancers, and HPV DNA is detected in ~100% of invasive squamous cervical cancers (4–6). HPVs are classified into high-, intermediate-, and low-risk types based on their association with invasive cancer. Types 16 and 18 are considered high-risk (oncogenic) types and are associated with aggressive forms of cervical cancers (7). Conversely, infection with low-risk HPV subtypes is unlikely to progress to invasive cancer (5).

HPV infection is the most common sexually transmitted disease, with reported prevalence rates of 19–46% (8–10). The major risk factor for HPV infection is sexual behavior, including early age at onset of sexual activity, multiple sexual partners, failure to use barrier methods of contraception, and coinfection with other sexually transmitted diseases, particularly HIV (11). The prevalence of HPV positivity declines with increasing age, and persistent infection after age 30 is usually associated with oncogenic types of HPV (12–14).

HPV infection disrupts the four-phased cell cycle during which cellular replication occurs. Chromosomal DNA is replicated during the S (synthesis) phase. In the M (mitosis) phase, the separation of duplicated DNA takes place. These two phases are separated by gap phases G\(_1\) and G\(_2\). Cells that are not dividing exit the cell cycle during the G\(_1\) phase and reside in a quiescent state or G\(_0\). To replicate, HPV must induce DNA synthesis in host cells in the quiescent phase and move them into an activated G\(_1\) phase. The HPV oncoproteins, E6 and E7, stimulate cell proliferation by interfering with the functions of the regulatory retinoblastoma protein and the p53 tumor suppressor protein. These cells undergo non-stop proliferation, eventually leading to premalignant changes and malignant transformation.

The progression of cellular changes that take place in HPV-infected cells has been described previously (15). The vast majority of HPV infections are transient because the host’s immune response rapidly eliminates the virus. However, women with chronic HPV infection tend to develop cervical abnormalities that progress from mild abnormalities to invasive cancer in susceptible cells of the transformation zone of the cervix (16). The aggressive forms of HPV can dramatically shorten time intervals between infection and neoplasia from years to months. Aggressive forms of HPV infection might also bypass the stages of progression so that invasive cancer arises de novo (14).

Determinants of risk for persistent infection and progression to invasive disease are not fully understood. Persistence of infection appears to be related to HPV type and concurrent infection with multiple viral types. As mentioned above, although prevalence of HPV infection is much lower among women over age 30, HPV infections at older ages tend to involve the oncogenic subtypes (16). Furthermore, HPV infection with lower viral load is more likely to persist in older women, suggesting reduced capability to clear the infection. Additionally, these older women are at increased risk for subsequent cervical dysplasia and cancer (10, 17). Reactivation of latent infection can also occur in women ages 55 and older (18). Another cofactor for cervical dysplasia and cancer is HIV infection, which disproportionately affects minority populations in the United States and elsewhere. AIDS induces pro-

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2 The abbreviations used are: HPV, human papillomavirus; BACCIS, Breast and Cervical Cancer Intervention Study; NCI, National Cancer Institute.
found immunosuppression and increased susceptibility to HPV persistence, as well as more rapid progression to invasive cervical cancer at younger ages. Among HIV-positive women, ~40% also have cervical dysplasia (19).

Environmental factors, particularly tobacco use, may also be important for persistence and progression of cervical dysplasia (20). Smoking has been associated with both cervical dysplasia and invasive cancer and is reported to increase the risk of HPV-associated malignant transformation (21). Smoking has also been reported as an independent risk factor for cervical cancer mortality within 5 years after diagnosis (22). Other studies suggest that micronutrient deficiency may contribute to progression of HPV-induced changes in the cervical epithelium (23, 24).

The role of inherited susceptibility to cervical cancer is uncertain. Goodman et al. (25) reported that the CYP1A1 Msp polymorphism may predispose to premalignant cervical lesions. After controlling for HPV type, certain HLA alleles have been associated with an increased risk of cervical cancer among Caucasian and African-American women (25–27). A study of 128 Latina women in New Mexico with high-grade dysplasia identified two HLA haplotypes associated with HPV-16 infection and other haplotypes that may protect against HPV type 16-associated cervical dysplasia (28).

Prevention of Cervical Cancer. Cervical cancer has been preventable since the introduction of the Pap smear in 1941. In developed countries, Pap smear programs have reduced cervical cancer deaths by 70% (29, 30). Microscopic examination of cells from the cervix can identify the progression of precancerous changes. Development of cervical cancer in the majority of women occurs over many years, so these precancerous changes can be observed, followed, and treated.

In the United States, standard of care for the evaluation of Pap smear abnormalities is colposcopy (examination of the cervix under magnification). The cervix is treated with acetic acid to visualize abnormal cells, and colposcopically directed cervical biopsies are performed. On the basis of biopsy results, low-grade abnormalities are followed for progression, whereas high-grade lesions and cancers are treated. Well-organized follow-up systems are critical for patients with dysplasia who are at risk for developing invasive cancer.

The role of HPV testing in the management of cervical disease is controversial. Because of the high prevalence of HPV infection in the absence of cervical disease, routine screening for HPV is not currently recommended. The ASCUS/LSIL Triage Study trial suggested that testing for cancer-associated HPV DNA can be used for women with Pap smears showing atypical squamous cells of undetermined significance (31). Additionally, HPV vaccines are under development, including vaccines for prophylaxis of HPV-free women, as well as therapeutic vaccines for infected women with cervical abnormalities (32).

Disparities in the Burden of Cervical Cancer. In the United States, benefits of early detection have not been shared by all segments of the population. Racial and socioeconomic disparities exist in cervical cancer incidence and mortality rates. Low income and minority women tend to be diagnosed at later stages and have higher mortality rates (33–40). Patients with stage I disease at diagnosis have an ~90% 5-year survival rate, whereas corresponding survival rates for stage II and III diseases are <50 and 10%, respectively (41). Patients with advanced disease at diagnosis (stage IV) also have more complications from hemorrhage, anemia, and radiation therapy.

After controlling for disease stage, race, ethnicity, and socioeconomic status, higher morbidity and mortality rates persist among underserved minority cervical cancer patients (29, 42, 43). Late stage at diagnosis, often identified as the major cause of excess morbidity and mortality in these populations, is the final result of complex interactions among multiple factors, including disparities in screening, diagnosis, and treatment, as well as other determinants that are not fully understood. As Parham and Hicks (44) stated in a 1998 editorial: “Assigning inferior outcome to late presentation accepts as given the very thing that needs explanation.”

Race, Ethnicity, and Immigrant Status as Determinants of Adverse Cervical Cancer Outcomes in the United States. In 1993, African-American women were twice as likely as Caucasian women to be diagnosed with cervical cancer and were two to three times more likely to die from their disease (3). More recent American Cancer Society data indicate that African-American women continue to have higher cervical cancer incidence and mortality rates (45). During the 1940s to 1980s, the incidence of cervical cancer in African Americans declined with increased Pap smear screening; however, cervical cancer still accounts for ~25% of cancer deaths in African-American women from certain urban populations (38). Although incidence rates plateau after age 40 among Caucasian women, cervical cancer incidence continues to rise with age among African-American women. Five-year survival rates among affected African-American women decreased from 64 to 59% between 1974 and 1994, whereas the corresponding survival rates among Caucasian women increased from 70 to 72% (46).

Hispanics, Native Americans, and many Asian American groups also have higher cervical cancer mortality rates than Caucasians (3, 47). Native Americans have the poorest cancer survival of any group in the United States, and preventable cancers are among the leading causes of death among Vietnamese Americans (48).

At first glance, race appears to be an important determinant of cervical cancer incidence and mortality. Howell et al. (49) and Greenwald et al. (50) reported race to be an independent predictor of cervical cancer survival. However, the effect of race on cancer outcome diminishes after accounting for socioeconomic status, comorbidity, and other factors (51). In fact, the National Health Interview Survey showed that income and education are better predictors of screening uptake than race and ethnicity (52). A study of African-American and Caucasian patients from an inner city hospital in Philadelphia found that racial differences in gynecologic cancer survival were attributable to differences in stage at presentation, socioeconomic status, and health insurance status. Stage-for-stage, there were no differences in survival among African-American and Caucasian women (53). In a study of military patients by Farley et al. (54), race was not an independent predictor of survival among patients with cervical carcinoma treated in an equal-access, unbiased, nonracial environment.

Non-English-speaking immigrant women face language and cultural barriers to Pap smear screening, including modesty, fatalism, and prohibitions against pelvic examination by male practitioners. Cultural factors can also contribute to mistrust of medical care providers (34, 35, 55), contributing to low screening rates. Furthermore, lack of culturally sensitive screening and treatment environments are barriers to early cancer detection among immigrant populations (56). The BACCIS study found low rates of Pap smear screening among non-English-speaking Latina and Chinese women, a finding that is generalizable to other immigrant populations (35).
Disparities in Cervical Cancer Screening and Treatment

Sociodemographic Characteristics and Access to Care for Cervical Carcinoma. Excess occurrences of cervical cancer, at least in African Americans, are largely restricted to older women who tend to have lower screening rates (57). The National Health Interview Survey found that nearly one-half of women ages 50–64 years did not obtain a Pap smear in the previous 3 years (37). Interestingly, the distribution of cervical cancer incidence in different ethnic populations exhibits different patterns by age group. For example, in the age group 55–69 years, Vietnamese women have the highest incidence, with a rate more than three times higher than Korean women, the second ranked group. In this age group, Hispanic women have the third highest incidence, followed by African-American women. Among women ages 30–54 years, however, Vietnamese women have the highest incidence rate, followed by Hispanic, and then African-American women (3). In the National Breast and Cervical Cancer Early Detection Program study of low-income women, only 60% of 312,858 women reported ever having had a Pap smear (58).

Cervical cancer screening, morbidity and mortality rates show large gaps between urban and rural populations. Using data of the Savannah River Regional Health Information System, Baker et al. (59) found the highest cervical cancer rates among rural African-American women over age 45 years. It has been shown that preventive care in primary care practices is often more difficult to deliver in rural as compared with urban medical practices, contributing to lower screening rates. Furthermore, rural women tend on average to be older, poorer, and less educated and, therefore, less frequently screened. These patients tend to spend less time with their physicians and more time traveling to their healthcare providers (60).

Several studies have reported that medically uninsured women have lower cancer screening rates and often present at later stages of disease. Compared with health maintenance organization-insured women, uninsured women tend to have later stages of cervical cancer diagnosis (22). Among Medicare patients with cervical cancer, those enrolled in health maintenance organizations are less likely than fee-for-service enrollees to be diagnosed with late-stage disease (61). In addition, Hiatt et al. (35) found that the strongest predictors of cancer screening were having private health insurance and frequent use of medical services.

Krieger et al. (62) found that incidence of cervical cancer is inversely related to socioeconomic status among all four racial/ethnic groups: Caucasian; African American; Asian/Pacific Islander; and Hispanic. In this study, poor and working-class Caucasian women had a cervical cancer incidence that was four times higher than in professional women of the same race (62). For several common forms of cancer, incidence rates varied more by socioeconomic status than by race/ethnicity. Liu et al. (63) also reported that socioeconomic status is inversely associated with cervical cancer incidence.

Minority women of low socioeconomic status tend to have comorbid diseases that contribute to poorer treatment outcomes for cervical cancer. One study of late-stage cervical cancer reported that Pap smear screening decreased with increasing numbers of comorbid conditions (64). Lower Pap smear screening rates translate into later stage at diagnosis and poorer outcomes. Comorbid diseases also contribute to suboptimal cervical cancer treatment. In fact, a study of racial differences in radiation therapy outcomes for cervical cancer found that the presence of comorbidity conditions was associated with reduced cancer-free survival (65). Similarly, Katz et al. (66) reported that African-American and low-income patients with government-funded insurance tended to have lower performance sta-
tus and receive lower radiation doses for cervical cancer than higher income Caucasian patients. Other studies found that low hemoglobin levels tend to be a significant predictor of poor treatment outcome; specifically, radiation therapy is less effective in anemic patients (67, 68) who are more likely to be from minority and underserved populations.

Access to quality healthcare service is often compromised among minority, rural, and other underserved populations. These populations have barriers to well-organized, quality Pap smear screening services, and often present with late-stage disease (56, 69). Surprisingly, African Americans in some areas of the United States have higher screening Pap smear rates (70) but are still diagnosed in later stages of disease and have higher mortality than Caucasians. One possible explanation for this is inadequate systems for follow-up of abnormal Pap smears. Reliability of Pap smear interpretation in many laboratories is another factor. Fals et al. (71) reported that New York City pathology labs were so overwhelmed with large volumes of work in the 1980s that some Pap smears were not read. Pap smears are performed in other geographic areas without an infrastructure for notification and follow-up of abnormal results. Equally concerning is the fact that studies have found that 27–70% of women with biopsy-proven high-grade dysplasia are lost to follow-up, thus delaying therapy (72, 73). In addition, minority and underserved populations are frequently faced with limited availability of treatment options and may not have access to expert medical care. Thom et al. (74) examined clinical determinants of survival in an inner city hospital and described the use of marginally adequate radiotherapy equipment.

Case management studies of ovarian and endometrial cancer have also shown that African Americans have substantially poorer survival rates when compared with their Caucasian counterparts. African Americans were treated less frequently and aggressively and were less likely to receive state-of-the-art therapy (75, 76). Studies of ovarian and other cancers have shown similar findings, indicating that lower survival rates among African Americans may be partly attributed to failure to receive standard of care (77, 78).

The Mundt et al. (65) study on racial differences in radiation therapy for cervical cancer reported that fewer African Americans received intracavitary radiation than Caucasian patients. Reasons for not receiving this treatment modality differed between African-American and Caucasian patients. Among African-American patients, patient refusals, comorbid conditions, and technical problems (poor geometry, inability to place tandem) were found, whereas Caucasians excluded from intracavity radiotherapy tended to have extrapelvic disease progression. This study did not indicate why technical problems were more common in African-American patients, and no explanations were given for refusal of intracavitary radiation by 11% of African-American patients. Comorbid conditions contraindicated therapy more often in African Americans than Caucasians, whereas poor compliance led to treatment interruptions in 28% of Caucasian patients and 10% of African Americans. Race was not a significant predictor of disease-free survival or cause-specific survival in multivariate analysis. Among African-American patients, poorer outcome was associated with lower hemoglobin levels at presentation and during treatment, comorbid disease, and low socioeconomic status (65).

Strategies for Reducing Cancer Disparities. As stated by Krieger et al. (79), “there is growing recognition of social class as an important determinant of cancer occurrence.” Economic inequality also contributes to racial/ethnic disparities in health
in the United States (79–81). Strategies are needed to improve prevention, diagnosis, and treatment of cervical cancer in under- served and minority populations. An important step to reducing disparities in cervical cancer screening is to identify women with high disease risk and low screening rates (i.e., low-income groups, older women, underinsured or uninsured women, ethnic minority populations, non-English speakers/ immigrants, and groups with cultural barriers to pelvic examinations). The specific barriers encountered by each group must be identified before behavior change can be implemented. To date, most studies examining socioeconomic status and race/ ethnicity have only compared African-American with Caucasian women. With the increasing diversity of the American population, broadening studies to diverse immigrant populations will further our understanding of differences in cervical cancer screening, diagnosis, treatment, and survival. In metropolitan areas, strategies must be developed that will be effective across ethnic groups (82). An early step is community-based research to develop and evaluate the new interventions. BACCIS (a Phase IV cancer control investigation of three related interventions designed to increase cancer screening) exemplifies a well-designed project specifically targeted to improve cancer screening knowledge, attitudes, and behavior among underserved, multietnic populations. Focus groups revealed that women in underserved target groups respond well to individuals that they trust and that many barriers could be addressed in one-to-one or small group interactions between outreach workers and women in the community (35). Targeted screening programs have been successful in certain groups. The Indian Health Service and the NCI-funded community-based Cancer Control Programs sponsored screening programs targeting Native American women > ages 60 in New Mexico and found that for more than two decades, the incidence rate of cervical cancer decreased by 66%, with a shift toward lower tumor stage (47, 83).

Concurrently, institutional systems issues also need to be examined (called inreach). Using a combined inreach-outreach approach similar to the BACCIS study, Paskett et al. (84) improved cervical and breast cancer screening rates among low income predominantly African-American women in North Carolina. Another aspect of inreach is to increase physician compliance with screening recommendations because lack of provider recommendation is a barrier to cancer screening (85). Additionally, quality standards mandated by the federal government for laboratories serving minority, rural and socioeconomic deprived women must be enforced (86).

To decrease the need for follow-up, one therapeutic approach is the see-and-treat approach to the management of cervical dysplasia, whereby colposcopy and treatment are performed in a single visit. The premise is that the fewer return visits needed for treatment, the lower the rates of loss to follow-up (87). Holscleret al. (88) performed a resource use analysis of see-and-treat in the management of high-grade squamous intraepithelial lesions and reported that this approach offered significant cost savings when compared with conventional management algorithms. This approach is reasonable not only for underserved United States patient populations but also in resource-poor areas worldwide.

Cost limitations constantly challenge healthcare institutions in underserved communities where relatively expensive cytology-based cervical cancer screening programs have been difficult to sustain. In a study of alternatives to screening, Goldie et al. (89) concluded that direct visualization of the cervix and HPV testing, combined with concurrent treatment, might provide more cost-effective alternatives to cytology and colposcopy for screening in low resource settings. Meissner’s (90) review of the literature on breast and cervical cancer screening interventions showed little consistency in outcome measures and widespread use of descriptive (rather than experimental) study design. Also, scientifically rigorous community-based intervention research needs to be disseminated; mechanisms are needed to diffuse intervention models into the public health infrastructure (90).

The NCI has established the Center to Reduce Cancer Health Disparities under the leadership of Dr. Harold Freeman, Chair of the President’s Cancer Panel. Additional research will seek to clarify the underlying causes of cancer disparities and develop strategies to improve cervical cancer screening and treatment in underserved and minority populations. The center held its first meeting in November 2001 to work on cervical cancer disparities. Follow-up meetings have continued to analyze the complex interaction of factors leading to these disparities. Subsequently, the July 2002 NCI Special Populations Networks Cancer Health Disparities Summit brought together experts in epidemiology, community health, statistics, and economics. An essential ingredient to future success is to increase levels of funding for research on cancer health disparities. It is hoped that this national attention, together with continued effort at the local and community level, will render cervical cancer disparities a problem of the past.

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