Prevention of Invasive Cervical Cancer in the US: Past, Present, and Future

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Abstract

Over the past several decades invasive cervical cancer (ICC) incidence in the US has declined dramatically. Much of this decline has been attributed to widespread utilization of cytology screening followed by treatment of precancerous lesions. Despite available technologies to prevent ICC and screening programs targeting high-risk women, certain populations in the US experience disproportionately high rates of ICC (e.g., racial/ethnic minorities and rural women). Limited access to and utilization of screening/follow-up services underlie this disparity. The licensure of the HPV vaccine in 2006 introduced an additional method of ICC prevention. Unfortunately, dissemination of the vaccine to age-eligible females has been lower than expected (32% have received all three recommended doses). Decreasing the burden of HPV infection and HPV-related diseases in the US will require greater dissemination of the HPV vaccine to adolescents and young adults, along with successful implementation of revised ICC screening guidelines that incorporate HPV and cytology co-testing. While a future without ICC is possible, we will need a comprehensive national healthcare program and innovative approaches to reduce ICC burden and disparities.

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Cervical Cancer Burden and Trends in the United States (US)

Invasive cervical cancer (ICC) and its precancerous lesions remain a costly public health problem in the US. In 2011, there were 12,710 new cases of ICC and 4,290 deaths due to the disease (1), making it the 13th most common cancer among women (2). Incidence and mortality rates have declined by more than 75% since the 1940s, a change attributed to the introduction and widespread utilization of ICC screening with cervical cytology (Papanicolaou [Pap]) and treatment of precancerous lesions (3). Since 1975, the age-adjusted incidence rate of ICC has fallen from 14.8 per 100,000 women to 6.6 in 2008 (4). This decline has been considered one of the greatest cancer prevention achievements in the US to date (3).

Disparities and the Excess Burden of Cervical Cancer

Although ICC incidence and mortality rates declined for the US as a nation, not all populations experienced similar declines and disparities persist (5, 6). Greater than 60% of ICC cases in the US occur in underserved populations (3), including racial/ethnic minorities, women residing in rural areas, and women living in poverty. Underserved women are less likely to undergo ICC screening and less likely to receive follow-up care, placing them at higher risk for the development of ICC (7, 8).

Racial/Ethnic Disparities

For decades, racial/ethnic minorities have experienced disproportionately higher rates of ICC than whites (Figure 1) (4). Since 1975, ICC incidence among black women has declined, yet in 2008 it remained 30% higher than that of whites (9.2 vs. 6.3 per 100,000). Although Hispanic women have experienced declining rates since 1990, the incidence of ICC (10.4 per 100,000)
remained higher than that of any other racial/ethnic group. American Indian/Alaska Native women have historically suffered from higher rates of ICC than white women; however, time trends are less clear given the small number of women comprising this population.

The age at which women are diagnosed with ICC differs by race/ethnicity. There is a sharp rise in incidence among black women with advancing age (Figure 2) (9). Among black women ≥ 85 years, the incidence of ICC was 28.9 per 100,000; this rate is three times that of white women. In contrast, as women of other racial/ethnic groups age, ICC incidence rates plateau or decline. It is unknown whether this age-related disparity is related to inadequate screening, or differences in socioeconomic factors or comorbid conditions (e.g., diabetes or hypertension) that may influence screening participation and follow-up.

**Geographic Disparities**

Regional variation in ICC incidence and mortality exists across the US, with disproportionately high rates concentrated along the US-Mexico border, in the Deep South, and in the Appalachian region (6). Underserved white women in Appalachia experience higher rates of ICC than white women outside Appalachia, illustrating that disparities extend beyond that of race/ethnicity. For example, in Ohio, ICC incidence and mortality are higher among white women in Appalachian counties (9.6 and 3.1 per 100,000, respectively) than among white women in non-Appalachian counties (7.7 and 2.3, respectively) (10).

**Socioeconomic Disparities**

In the US, cancer registries lack information on socioeconomic status (SES), making it difficult to report ICC incidence by SES. While epidemiologic research on SES and its
association with ICC has been complicated by issues of race/ethnicity, studies have shown SES to be a strong predictor of ICC screening, diagnosis, and treatment, even after controlling for race/ethnicity (11). Further studies are needed to examine how SES impacts ICC rates, and elucidate the role of race/ethnicity.

**Cervical Cancer Screening**

ICC and its precancerous lesions are effectively detected by routine Pap tests. The excess burden of ICC among high-risk populations may be partly explained by an underutilization of screening services. High-risk women may not have adequate access to screening, may not receive physician recommendation for screening (12), or may choose not to participate in these services. Poverty, lack of health insurance, cultural beliefs and perceptions, fear, embarrassment, lack of knowledge, language differences, and immigration status are among many barriers preventing women from being screened (13, 14).

**Cytology Screening Coverage**

Rates of cytology screening are comparable across racial/ethnic groups, albeit slightly higher among minorities (Figure 3) (15). Paradoxically, although screening rates among black (86.1%) and Hispanic (84.3%) women are slightly higher than among white women (81.9%), ICC incidence and mortality rates remain higher among black and Hispanic women. For white women, screening is lower among those residing in Appalachian Ohio (77.8%) compared to those in non-Appalachian Ohio (82.5%), demonstrating that poor, underserved white women underutilize cervical screening.
Availability, Utilization, and Timeliness of Treatment Services

Timely diagnostic follow-up of abnormal results and the availability and utilization of treatment services are needed to effectively reduce ICC (7, 8). Uninsured women and racial/ethnic minorities experience the longest delays in cervical disease evaluation, often due to a lack of health insurance and site of care (16). Federal and state funding for health-related services among the underserved often exclude high-risk populations such as recent or undocumented immigrants, preventing access to follow-up treatment (3, 17, 18). Among Appalachian women in Kentucky, logistical issues are the most common barriers to ICC follow-up and treatment, including lack of transportation, scheduling appointments, and uncertainty regarding medical procedures (3). Similar difficulties have been reported by Latina women, including cost, inability to obtain childcare, and fear of the procedure/outcome (3, 19). Physicians have cited reduced funding for follow-up colposcopy and treatment as key issues (17).

Policy Initiatives to Improve Cervical Screening Coverage

Federally and locally funded ICC prevention programs have been implemented to promote screening among high-risk women. The Breast and Cervical Cancer Mortality Prevention Act (1990) established the only nationwide screening program, the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), which provides access to screening and diagnostic services for all low-income, uninsured, and underinsured women (20). However, only a small proportion of financially eligible women receive services due to severe funding limitations. Between 2004 and 2006, only 8.7% of eligible women ages 18-64 were screened for ICC (21). This percentage varies by age, state, and race/ethnicity, from 6.5% in blacks to 36.1%
in American Indians/Alaska Natives (21). Some women diagnosed with ICC through the NBCCEDP have had access to treatment since 2000 through the Breast and Cervical Cancer Prevention and Treatment Act. Since the NBCCEDP specifically targets underserved women, the program is in a unique position to address issues of access to screening and treatment services. However, decreasing the ICC burden will require increased national funding to support the NBCCEDP, not only to provide Pap tests to all eligible women, but also to assure follow-up of abnormal results.

**Human Papillomavirus (HPV) Vaccination**

Currently, there are two ICC prevention methods: cervical screening followed by treatment of precancerous lesions and HPV vaccination. In 2006, the first HPV vaccine (quadrivalent; Gardasil) was licensed in the US for use among young females (9-26 years), and in 2009, another HPV vaccine (bivalent; Cervarix) was licensed, also for use among young females (10-25 years).

**HPV Vaccination Coverage Among Females**

Since 2006, HPV vaccination coverage in the US has increased among adolescents, nevertheless coverage remains low. Findings from the 2010 National Immunization Survey-Teen (NIS-Teen) indicate that slightly less than half of adolescent girls (13-17 years) received at least one dose of the HPV vaccine (quadrivalent or bivalent), and only 32% received all three recommended doses (Figure 4a) (22). Vaccination coverage varied by race/ethnicity (Figure 4b) (22); initiation (≥1 dose) among whites (45.8%) was significantly lower than among Hispanics (56.2%) or American Indians/Alaska Natives (64.8%).
The HPV vaccine lags behind other adolescent vaccines. In 2010, 91.6% of adolescents received three recommended doses of Hepatitis B vaccine, whereas only 32% of adolescent females received three recommended doses of HPV vaccine (Figure 5) (22). Efforts are needed to improve HPV vaccine initiation and completion, especially among racial/ethnic minorities at higher risk of ICC.

Barriers to HPV Vaccination

Numerous barriers impeding HPV vaccine uptake have been identified. Among adolescents and young adults, common individual barriers include cost, safety, and the perception that vaccination is unnecessary if not sexually active (23, 24). Parental knowledge, attitudes, and beliefs regarding vaccine also influence uptake (25, 26). Parents opposing the vaccine reported that their children were too young, the vaccine was not needed, children were not sexually active (27-29), and that receipt of vaccine might increase promiscuity (17, 30, 31). Moreover, the media and public officials have made unsubstantiated claims regarding vaccine safety, reinforcing negative opinions of the HPV vaccine (32).

Institutional/structural factors that influence vaccine initiation include cultural/linguistic differences, lack of healthcare access, and lack of physician recommendation. Among minority populations, language difficulties and navigating a complex healthcare system pose considerable challenges to vaccination. Poor access to health services also negatively impacts vaccine uptake. A study in Kentucky found a seven-fold decrease in rural women, versus urban women, returning for a follow-up vaccine dose despite provision of the vaccine at no cost. These findings suggest that distance to the clinic might influence completion rates (33). Insurance status, lack of
awareness among those who are eligible for free/discounted vaccines, and lack of a steady primary care source also impact vaccine uptake (23, 34-36).

Findings from the 2010 NIS-Teen survey indicate that physician recommendation of HPV vaccine is a key factor in vaccine initiation (27). Many primary care physicians have not been proactive in promoting the vaccine particularly to young adolescents, the target age for vaccination. In a national study of family physicians, pediatricians, and obstetricians/gynecologists (37), all were least likely to recommend the HPV vaccine to 11-12 year olds (34.6%) compared with 13-17 year olds (52.7%) and 18-26 year olds (50.2%). Other physician-related factors include missed opportunities for catch-up vaccination during routine health visits, vaccine cost and reimbursement, and difficulty discussing sexuality with adolescents (17, 38).

Policy Initiatives to Promote HPV Vaccination

One year post-licensure, the Advisory Committee on Immunization Practices (ACIP) recommended routine HPV vaccination for young females (39). With recommendations from ACIP, physicians are more likely to promote the HPV vaccine to patients and costs are covered by many health insurance plans. In addition, eligible children can receive the HPV vaccine at no cost through the federally funded Vaccines for Children (VFC) program that provides free ACIP-recommended vaccines to children (≤18 years) unable to pay (e.g., Medicaid eligible, uninsured/underinsured, American Indian/Alaska Native) (40). Therefore, in theory, most young women ages 9-18 can receive the HPV vaccine at little or no cost. Still, there are populations who lack health insurance but are ineligible for VFC and cannot afford the cost of the vaccine or...
Clinic administration fee. Cost may be a more important barrier to vaccination among those already at increased risk of HPV infection and ICC.

An additional strategy to reduce ICC among females has been HPV vaccination of males. HPV infection in men contributes to HPV infection and subsequent development of ICC in women (41). Vaccinating males reduces HPV transmission to females and strengthens herd immunity. Model-based studies have demonstrated that a gender-neutral HPV vaccination strategy would result in maximal disease reduction (42, 43). Given the low vaccine coverage among US females, HPV vaccination has recently been recommended for routine use among males. In 2009, the quadrivalent HPV vaccine was approved for use among young males (9-26 years), and in 2011 ACIP officially recommended routine HPV vaccination of both girls (bivalent or quadrivalent) and boys (quadrivalent) ages 11-12 years. With ACIP recommendations in place and VFC coverage ensured for both genders, physician recommendation and health insurance coverage of the HPV vaccine should improve over time, expanding accessibility to all young women and men in the US.

Reducing the Burden of Cervical Cancer in the US

A more thorough understanding of the etiologic role of HPV has provided the foundation for rational, targeted, and cost-effective approaches to ICC prevention. HPV vaccination and HPV-based screening hold promise for eliminating disease and disease-related disparities. Universal vaccination against HPV has the potential to reduce the incidence of ICC and its precancerous lesions (grade 2/3) by 91% (42). However, continued efforts are needed to advocate for HPV vaccination among adolescents and young adults, especially among racial/ethnic minorities at increased risk of ICC. New approaches should be considered to
broadly disseminate HPV vaccines. History shows that incorporating vaccination into school entry requirements ensures high vaccination coverage in the US. Campaign strategies should also encourage increased knowledge and awareness of HPV vaccination, and improve physician recommendations. With every healthcare visit is the opportunity to vaccinate.

Increased knowledge of HPV natural history and carcinogenesis has led to improved ICC screening methods, including HPV DNA testing. In March 2012, several US professional organizations released updated, evidence-based cervical screening recommendations that incorporate routine HPV testing (44, 45). For women ages 30-65, HPV co-testing (cytology + HPV test) should be performed every 5 years, or cytology alone every 3 years. Additional recommendations include: 1) women ages 21-29 should undergo cytology every 3 years; 2) certain low-risk groups should no longer be screened (women under age 21, certain women over age 65, and women who have undergone complete hysterectomy); and 3) women vaccinated against HPV should continue to follow screening guidelines. Through the extension of screening intervals and reduced screening of low-risk women (e.g., adolescents, and older women without history of ICC), fewer instances of overscreening and overtreatment should occur (44).

While universal healthcare does not exist in the US, healthcare in general is undergoing rapid change. Under the Affordable Care Act (2010), women will be able to receive recommended preventive services – including cervical screening and adolescent HPV vaccination – without cost sharing (copayment, co-insurance, or deductible) (46), a great stride in improving the affordability and accessibility of ICC prevention for women. Nevertheless, many questions will need to be addressed as we implement the ACA, including: What infrastructure will be required for successful implementation? How do we incorporate revised ICC screening guidelines (e.g., extended screening intervals and routine HPV testing) into current screening
programs? Should HPV testing be offered in an alternative sequence (e.g., HPV testing as a primary screen with cytological triage of HPV+ women (47-51))? At which age could screening initiation be further delayed? How do we minimize overscreening and overtreating HPV+ women? How should screening guidelines be modified as vaccination rates improve?

In summary, ICC can be eliminated in the US. To achieve this goal the US will need to adopt a comprehensive national healthcare program that underscores accessible and equitable healthcare, and delivers compassionate care to all. With the implementation of the ACA, this type of healthcare is possible. Interest in women’s health has been renewed, and the US is poised to make even greater progress in cervical cancer prevention and early detection. Through the development of a national ICC control strategy, we can decrease the number of women infected with HPV, increase access to care and improve cancer-related outcomes, and lastly, decrease health disparities. A future without ICC is possible, though we must be innovative and vigilant in our approach to reducing ICC burden and disparities.
Acknowledgements

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Conflicts of Interest

AR Giuliano receives grant funding from GSK and Merk & Co., Inc. She is a consultant to Merck Research Laboratories and is on the Speaker Bureau of Merk & Co., Inc. ED Paskett receives grant funding from Merk & Co., Inc. All other authors report no conflicts of interest.
References


Figure 1. Time trends in age-adjusted incidence\textsuperscript{a} of invasive cervical cancer in the US, 1975-2008, by race/ethnicity.

\textsuperscript{a}Rates are age-adjusted to the 2000 US Standard Population. Incidence data for whites and blacks are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics are from the SEER 13 Areas (SEER 9 Areas, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).

\textsuperscript{b}Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry.

\textsuperscript{c}Rates for American Indian/Alaska Native are based on the CHSDA (Contract Health Service Delivery Area) counties.

Notes: SEER 9 and SEER 13 cancer incidence data are collected from population-based cancer registries covering 9.5\% and 13.8\% of the US population, respectively.

Source: Surveillance, Epidemiology, and End Results (SEER) (4).
Figure 2. Age-specific incidence\textsuperscript{a} of invasive cervical cancer in the US, 2000-2008, by race/ethnicity.

\textsuperscript{a}Incidence data are from the SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey).

\textsuperscript{b}Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry.

\textsuperscript{c}Rates for American Indian/Alaska Native are based on the CHSDA (Contract Health Service Delivery Area) counties.

Notes: SEER 17 cancer incidence data are collected from population-based cancer registries covering 26.2% of the US population.

Source: Surveillance, Epidemiology, and End Results (SEER) (9).
Figure 3. Estimates of recent, self-reported Pap screening among adult women\(^a\) in the US, 2010.

\(^a\)Women 18 years of age and older with an intact cervix who have had a Pap test within the past 3 years.

\(^b\)Estimates are from Ohio counties considered part of the Appalachian region.

\(^c\)Estimates are from Ohio counties not considered part of the Appalachian region.

Notes: BRFSS data are collected by each state via landline telephone survey. The median response rate for the 2010 BRFSS (all states combined) was 54.6%. BRFSS prevalence estimates are overestimated when compared with National Health Interview Survey (NHIS) estimates.

Figure 4. A, estimates of HPV vaccination\textsuperscript{a} coverage among adolescent girls (13-17 years) in the US, 2010. B, estimates of HPV vaccination\textsuperscript{a} coverage among adolescent girls (13-17 years) in the US, 2010, by race/ethnicity.

\textsuperscript{a}Quadrivalent or bivalent vaccine.

Figure 5. Estimates of childhood vaccination coverage among adolescents (13-17 years) in the US, 2010.

Abbreviations: HPV, human papillomavirus vaccine; MenACWY, meningococcal vaccine; Td/Tdap, tetanus toxoid-diphtheria vaccine (Td) or tetanus toxoid, diphtheria, pertussis vaccine (Tdap); MMR, measles, mumps, rubella vaccine; HepB, hepatitis B vaccine.

Notes: HPV vaccine (quadrivalent or bivalent) reported among females only.

Figure 3
**Figure 4**

**A**

48.7% of adolescent girls aged 13-17 years received at least 1 dose of the HPV vaccine.

32% received all 3 recommended doses.

**B**

HPV Vaccination Coverage (%) by Race/Ethnicity:

- White: 45.8%
- Black: 48.9%
- Hispanic: 56.2%
- Amer. Indian/AK Native: 64.8%
- Asian/PI: 50.1%

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Figure 5

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Coverage (%)</th>
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<tr>
<td>HPV (1 dose)</td>
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<td>MenACWY (1 dose)</td>
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<td>Td/Tdap (1 dose)</td>
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<td>MMR (2 doses)</td>
<td>90.5</td>
</tr>
<tr>
<td>HepB (3 doses)</td>
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