

# Assessing the Short-term and Long-term Burden of Illness in Cervical Cancer

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**W**hen assessing the burden of illness for cervical disease, it is often assumed that invasive cervical cancer accounts for the majority of costs. In reality, the effects of cervical cancer and cervical dysplasias are diverse and encompass direct and indirect costs that result from frequently overlooked factors related to secondary prevention methods and quality-of-life (QOL) issues.<sup>1</sup> The importance and impact of these direct and indirect costs vary by audience in the managed care setting. Direct costs may be more relevant to payers such as managed care plans because increasing medical expenditures affect them immediately. Payers must also remain cognizant of indirect costs and QOL issues. These may influence patients' compliance with screening and follow-up care for cervical abnormalities, further affecting outcomes and costs. Purchasers such as employers maintain a relatively uniform interest in direct and indirect cost data and QOL burden because all of these components—particularly productivity issues and absenteeism—can profoundly impact their bottom line.

## Human Papillomavirus Infection

A brief review of human papillomavirus (HPV)—so-called because it causes benign warts or papillomas—and its associated diseases sheds light on why healthcare professionals and the public are paying increased attention to cervical cancer prevention. More than 100 strains of HPV have been identified, and more than 30 of these infect the genital mucosa, 15 of which are oncogenic or cancer-causing.<sup>2</sup> It is a popular misconception that sexual penetration is required to transmit HPV. Although sexual activity appears to be the primary mode of transmission, skin-to-skin contact between surface areas harboring HPV is all that is needed to transmit the virus. Therefore, condoms are not universally effective in preventing transmission. Infection is frequently asymptomatic, and the absence of obvious signs of infection increases the potential for unwitting disease transmission.

Although most HPV infections resolve spontaneously within approximately 12 to 18 months, the virus may only be quiescent, and those previously exposed may redevelop the infection later. Research shows that only 50% of women develop a systemic immune response to infection, likely because the usual immune response triggers (inflammation) do not occur with HPV infection.<sup>3</sup> This lack of

## Abstract

Human papillomavirus (HPV) infection is associated with significant clinical, social, and financial burdens. Infection is often asymptomatic, which increases the risk of unwitting transmission. Up to 29 million American women between the ages of 14 and 59 years are currently infected, and 80% of women will contract the infection by 50 years of age.

Persistent oncogenic HPV infection is the leading cause of cervical dysplasia and neoplasia, and evidence shows that oncogenic HPV is present in 99.7% of cervical cancer specimens. Cervical cancer and cervical dysplasias are responsible for the vast majority of morbidities and deaths associated with HPV-related illness. The direct annual healthcare costs for screening, treating, and managing abnormalities related to cervical cancer and cervical dysplasias in the United States are estimated to be as high as \$4.6 billion.

Although the direct costs of cervical cancer are substantial, only 10% of all expenditures derive from invasive disease; more than two thirds of the total cost is attributable to screening and testing. Annual indirect costs resulting from lost productivity and loss of earnings due to premature death are also significant and are estimated to be higher than direct costs.

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immune response may be explained in part by the fact that memory cells are located in the lymphatic system and not in the mucosa at the site of HPV infection. The resulting absence of memory cells for the infecting HPV type allows for repeated infections with the same HPV type and others; in simplest terms, the level of potential natural immunity against HPV is under significant debate.<sup>3</sup> Some HPV infections persist for many years, and these persistent infections are associated with more serious sequelae, such as cervical cancer. HPV infection correlates with genital warts, cervical intraepithelial neoplasia (CIN), and invasive cervical cancer, all of which produce significant morbidity and, in the case of cervical cancer, mortality.<sup>4</sup> Persistent oncogenic HPV infection is the leading cause of cervical dysplasia and neoplasia; evidence shows that oncogenic HPV is present in 99.7% of cervical cancer specimens.<sup>2</sup>

#### **Incidence, Mortality, and the Role of Secondary Prevention**

The National Cancer Institute estimates that more than 6 million new genital HPV infections occur annually.<sup>2</sup> Almost 24.9 million women aged 14 to 59 years in the United States are actively infected, and 80% of sexually active women will contract genital HPV by 50 years of age.<sup>2</sup> It is estimated that between 64% and 82% of sexually active adolescent girls will test positive for HPV, and it is believed that sexually active males in the same age group are similarly infected.<sup>2</sup> More than 50% of these infections are caused by oncogenic virus types.<sup>2</sup>

HPV is responsible for 5.2% of all cancers worldwide.<sup>2</sup> Whereas HPV types 6 and 11 are associated with 10% of cases of low-grade or low-risk lesions and 90% of cases of genital warts, oncogenic HPV types 16 and 18 account for ~76% of all cases of high-grade CIN or dysplasias and invasive cervical cancer in the United States.<sup>5</sup> Cervical cancer represents 9.8% of all cancers in women.<sup>2</sup>

Secondary prevention methods, such as Papanicolaou's cervical smear (Pap test), have dramatically reduced the incidence of cervical cancer and its associated mortality, yet cervical cancer continues to be diagnosed in more than 11,000 women annually in the United States, and 4000 die each year from the disease (1 woman every 2.5 hours).<sup>6</sup> A greater proportion of younger women die from

cervical cancer than from other gynecologic cancers, with a reported 26 years of life lost per woman because of death from cervical cancer in the United States as compared with 19 for breast cancer and 18 for ovarian cancer.<sup>7</sup> The prevalence of cervical cancer in a younger population is of significant concern to healthcare plans and employers, particularly as it relates to increased medical costs and lost workdays for younger employees.

When cervical cancer is diagnosed at the dysplasia stage, it has a nearly 100% cure rate, making early detection very important to those involved in managed care.<sup>8</sup> Secondary prevention efforts, such as routine screening programs, have significantly reduced the incidence of cervical cancer and subsequent mortality. At one time, cervical cancer was the leading cause of cancer death for women, but the cervical cancer mortality rate declined 74% between 1955 and 1992 and it now ranks fifteenth, presumably as a result of the implementation of secondary prevention initiatives and related improvements.<sup>8</sup> Although improvements to secondary prevention methods are ongoing, their impact appears to have plateaued. There has been no noticeable improvement in screening adherence rates in the past 6 years, and among participants in commercial health plans, it has remained at ~80% since 2001.<sup>9</sup> Screening efforts have presumably led to the decline in cases of cervical squamous cell carcinoma, but the incidence of cervical adenocarcinoma has been increasing.<sup>10</sup> This increase may result from the Pap test's inefficiency in detecting adenocarcinoma or a greater number of oncogenic HPV infections in younger women.<sup>10</sup> Without expanded employment of preventive measures such as vaccination, the rates of cervical cancer and cervical dysplasia may rise in response to these screening inefficiencies and a growing number of HPV infections.<sup>2,8,9</sup>

The impact of cervical cancer and cervical dysplasia on managed care can be characterized by the disease stage at the time of diagnosis. The rate of various abnormalities diagnosed through routine screening and false-positive test results can have a significant effect on the burden of illness. In one managed care population, ~5% of women undergoing routine screening had an abnormal Pap test in 1998.<sup>11</sup> Of these women, the peak incidence of CIN 1 was 5.1 per 1000 women aged 20 to 24 years and the peak incidence of CIN 2/3 was 8.1 per 1000

women aged 25 to 29 years, indicating a slightly higher incidence of more serious lesions in the older age group.<sup>11</sup> This notable rate of precancerous lesions in young women inevitably translates into significant costs for managed care organizations (MCOs). Follow-up of abnormal Pap tests found CIN 1/3 or cancer in only 19.4% of patients, demonstrating the test's potential for producing false-positive results that may require unnecessary follow-up and lead to excessive expenditures.<sup>10</sup> A total of 51% of abnormal Pap tests produced false-positive results, and 29% of women underwent inadequate follow-up procedures according to accepted management guidelines. These factors indicate that some increased costs relate to screening methods rather than the disease itself.<sup>11</sup>

### Quality-of-life Burden

The potential of HPV infection to lead to mortal conditions can have a pronounced impact on a patient's QOL in the managed care setting, particularly when abnormal Pap test results suggest cervical cancer.<sup>12</sup> Fleurence et al reviewed studies on the impact of abnormal Pap tests, diagnosis of HPV infection, and cervical cancer on patients' health-related QOL (HR-QOL).<sup>12</sup> Of the 5 studies on abnormal Pap tests included in this analysis, 2 reported that patients experienced increased worrying or anxiety after receiving abnormal results.<sup>12</sup> One study performed a 5-year follow-up survey and found that women who received abnormal Pap test results but did not comply with a scheduled colposcopy developed significantly more worries ( $P = .002$ ), greater impairment of daily activities ( $P = .02$ ), worse moods ( $P = .01$ ), impaired sleep ( $P = .004$ ), and impaired sexual interest ( $P = .03$ ).<sup>12</sup> A third study found that some women had specific concerns about the possibility of having cervical cancer and their scheduled colposcopy procedure.<sup>12</sup> In another study, nearly half of the women interviewed prior to their first follow-up visit after receiving abnormal Pap test results reported decreased sexual frequency.<sup>12</sup>

All 5 studies reviewed by Fleurence et al assessed the impact of a diagnosis of HPV infection on HR-QOL and concluded that women experienced a great deal of anxiety and concern about their diagnosis,<sup>12</sup> as well as anger, shame, guilt, a decline in self-esteem, and a more negative body image. In

4 of the 5 studies on HPV-infection diagnosis, women reported negative changes in their sexual relationships.<sup>12</sup> To date, 14 different studies have assessed the effects of cervical cancer on women. Some of the more persistent concerns women with cervical cancer expressed include quality of care, functional and work issues, and relationship and sexuality concerns, all of which had a moderately negative impact on their HR-QOL. Short Form-36 scores were significantly lower than age-specific expected mean values in all scales.<sup>12</sup>

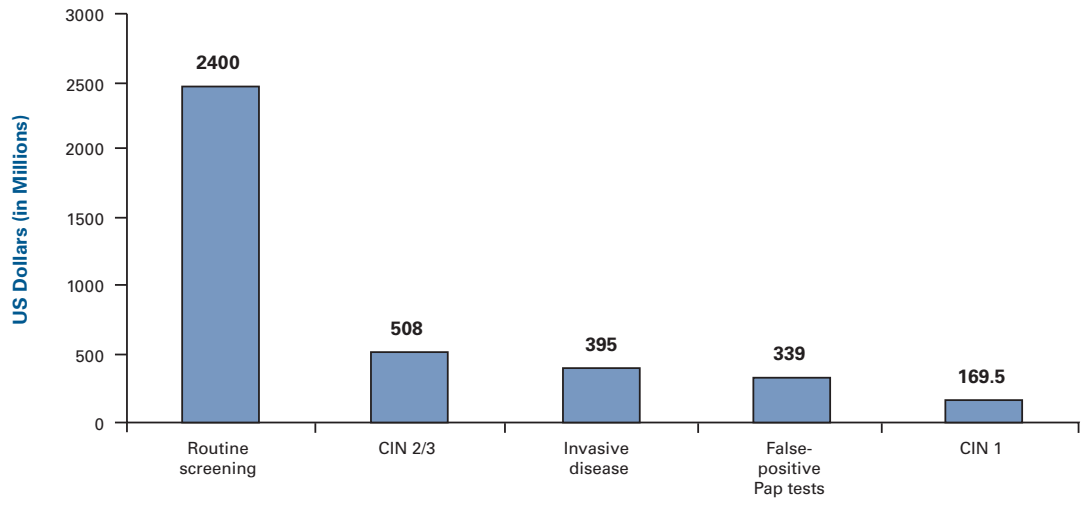
Women who underwent surgical treatment for cervical cancer reported sexual problems as the greatest detractor on QOL.<sup>12</sup> Their psychological well-being, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30, was far below normative after surgery, and scores continued to decline 3 months after the procedure. Women undergoing radiotherapy reported persistent sexual dysfunction and adverse vaginal changes, which continued for 2 years following treatment.<sup>12</sup> A significant proportion of women who underwent surgical treatment for cervical cancer experienced fertility loss or a loss in the ability to carry their pregnancy to term.<sup>13</sup>

Depression and a decline in emotional functioning are most acute in cervical cancer survivors just after receiving the diagnosis. Other gynecologic cancer survivors reach precancer QOL levels after treatment, but for cervical cancer survivors, sexual functioning often remains moderately decreased for a prolonged period.<sup>12</sup>

### Economic Burden: Direct Costs

In addition to psychological burdens, significant economic burdens are associated with HPV-related disease, including direct and indirect costs. The focus of MCOs is clearly on direct medical costs. The vast majority of these costs are related to routine screening, follow-up of abnormal Pap tests, and treatment of dysplasia.<sup>1</sup> Estimates in 2005 US dollars of the direct healthcare costs of cervical cancer in the United States were as high as \$4.6 billion annually.<sup>1,12</sup> Although various studies' estimates for direct costs related to sexually transmitted diseases differed somewhat according to the methodology used, even the lowest determination of HPV-related disease spending placed it second only to human immunodeficiency virus (HIV) spending. Direct

■ **Figure 1.** US Annual Direct Cost Estimates for Cervical HPV-related Disease (2005)



HPV indicates human papillomavirus; CIN, cervical intraepithelial neoplasia.  
 Source: Reference 1.

costs in 2004 US dollars for HPV-related disease exceeded spending for genital herpes (\$1.9 billion) and Chlamydia (\$2 million-\$3 billion) and came in fourth overall among direct costs for all infectious diseases, behind HIV, nosocomial infections, and food-borne bacterial infections.<sup>14</sup> In addition to the \$4.6 billion (in 2005 US dollars) in direct health-care costs for cervical cancer and cervical dysplasias, the costs of anogenital warts and other cancers associated with oncogenic HPV contribute a small amount to the annual, direct expenditures of HPV-related disease, raising the total economic burden to as high as \$5 billion (in 2006 US dollars).<sup>1,12</sup> The most conservative estimates of direct annual costs (in 2005 US dollars) for HPV-related cervical disease are \$2.4 billion for routine screening, \$339 million for false-positive Pap tests, \$169.5 million for CIN 1, \$508 million for CIN 2/3, and \$395 million for invasive disease (Figure 1).<sup>1</sup> These cost estimates do not account for some of the newer secondary prevention technologies, such as liquid-based cytology and HPV DNA testing, in which specimens are collected at the physician's office and subsequently analyzed by a pathologist.<sup>14</sup>

In designing a cost-effectiveness model for alternative triage strategies for atypical squamous cells (ASC) of undetermined significance, Kim et al established baseline values for the average costs associated with various secondary prevention methods.<sup>15</sup> For conventional cervical cytology screening

(Pap tests), researchers estimated the average per-case procedural cost to be between \$58 and \$94 (in 2000 US dollars), including \$15 for a normal test result and \$51 for an abnormal result with physician review.<sup>15</sup> When using the more advanced ThinPrep liquid-based test, Kim et al estimated these costs would increase to \$22 and \$64 for normal and abnormal test results, respectively. The researchers also estimated office visit and time costs associated with both tests to be \$22 and \$21, respectively.<sup>15</sup> A newer secondary screening method with HPV DNA testing using the Hybrid Capture II system was estimated to cost \$48.50 on average.<sup>15</sup>

Annual direct medical costs for follow-up monitoring and treatment of various abnormal cytologic findings on routine Pap tests are estimated to be \$400 million for ASC, \$50 million for atypical glandular cells, \$600 million for low-grade squamous intraepithelial lesions, and \$250 million for high-grade squamous intraepithelial lesions.<sup>1</sup> Insinga et al examined medical and laboratory claims and cost data from a single MCO to determine resource utilization and costs associated with cervical cancer.<sup>1</sup> Data were extracted from the records of 103,476 women enrollees who obtained any service related to screening or treatment for cervical cancer between 1997 and 2002, and costs were adjusted to 2005 US dollars.<sup>1</sup> The study reported the mean cost of an episode of care after an abnormal routine cervical test as \$732, compared

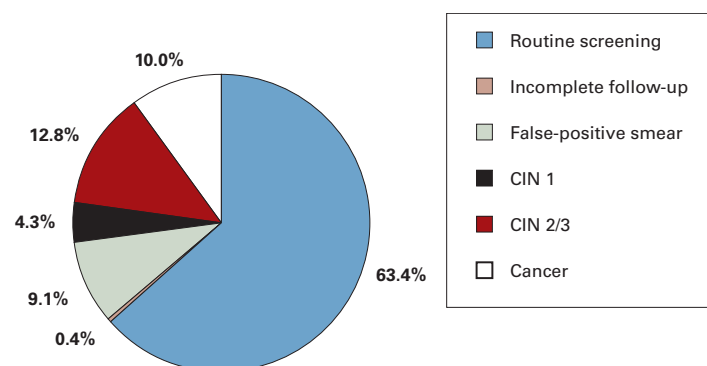
with \$57 for a normal result. As one might expect, mean costs of care increased in correlation to rising grades of initial cytologic abnormality, from \$299 for ASC to \$2349 for a high-grade intraepithelial lesion. A second study estimated the annual direct costs for following up abnormal cervical cytologic findings and treating neoplasia at \$3.5 billion (in 2005 US dollars).<sup>14</sup>

Insinga et al also found that patients used additional resources as a result of abnormal findings, including more treatment visits (2.6 vs 6.6) and Pap tests (2.3 vs 3.7).<sup>1</sup> The duration of follow-up also increased from 7.4 to 17.4 months for patients with abnormal test results.<sup>1</sup> Women with combined CIN 1/3 averaged a mean of 7.2 visits, 4.2 Pap tests, and 19.9 months of follow-up. Annual plan costs for screening and treating cervical cancer were \$26,415 per 1000 enrolled women.<sup>1</sup> Routine screening accounted for \$16,746 annually; CIN costs totaled \$4535; and cervical cancer, \$2629. The bulk of these costs were associated with testing and following up on abnormal test results, as opposed to dealing with invasive cervical cancer. Costs for women aged 20 to 29 years peaked at \$51,863 per 1000 enrolled women, nearly double the peak costs for women 50 to 69 years of age.<sup>1</sup>

Of particular interest was the effect of false-positive test results on MCOs. Each false-positive Pap test resulted in a mean of 3.3 visits, 2.6 Pap tests, and 10.3 months of follow-up care.<sup>1</sup> Resource utilization was greater for patients with false-positive Pap tests than for patients with a finding of ASC. Estimated false-positive rates can be as high as 30.5%, adding considerable unnecessary costs.<sup>1</sup> The study by Insinga et al found that 9% of expenditures were for following up on false-positive Pap test results, producing an annual cost of \$2394 per 1000 enrolled women—an amount almost equal to that for women with invasive cancer.<sup>1</sup>

Insinga et al conducted another study examining the cost of cervical disease. This analysis estimated annual costs for all cases of CIN at \$2.3 billion (in 2005 US dollars), and the costs for cervical cancer totaled \$300 million. This estimate for CIN is significantly higher than that in Insinga et al's first study. A critique of the second study noted that it based the annual incidence of CIN on the number of self-reported yearly Pap tests in a national health survey and the number of abnormal findings

■ **Figure 2.** Distribution of Cervical HPV-related Disease Costs in a Commercial Health Plan



HPV indicates human papillomavirus; CIN, cervical intraepithelial neoplasia.

Source: Reference 1.

reviewed by pathology laboratories, both of which were likely overestimated because of over-reporting of Pap tests and sample bias in the laboratories.<sup>14</sup> The study also estimated the direct lifetime costs of HPV-related disease and the annual costs of all abnormal Pap tests to total \$4.6 billion (in 2005 US dollars). This includes costs for an estimated 30% false-positive rate.<sup>14</sup>

In reviewing direct costs associated with cervical cancer and cervical dysplasias, the allocation of money and resources for preventing and treating cervical cancer is particularly noteworthy. Intuitively, managed care stakeholders often associate the majority of cancer costs with chemotherapy, surgery, and radiation treatment of invasive disease. The costs for cervical cancer, however, are primarily for prevention and early detection, not treatment. Routine cancer screening accounts for nearly two thirds of total annual expenditures, and an additional 17% is dedicated to the management of cervical precancers; only 10% is used in the treatment of invasive cancer (Figure 2).<sup>1</sup>

Additional interventions that offer primary prevention, such as HPV vaccination, may serve to overcome some of the vast costs allocated to secondary prevention methods and follow-up. Although effective screening programs have greatly reduced the number of cervical cancers diagnosed in the United States, no program is 100% effective. Despite the great economic burden of cervical cancer prevention and diagnosis through screening, it is estimated that 55% to 60% of cases of cervical cancer are diag-



nosed in women who have not undergone a Pap test in the previous 3 years.<sup>1</sup> Primary prevention in the form of HPV vaccination may help minimize the shortcomings of current secondary prevention methods (screening) and, in turn, minimize costs.

### Economic Burden: Indirect Costs

Indirect costs, including lost productivity and lost future earnings, account for a significant portion of the total costs for all cancers, particularly those in the later stages, which are associated with higher mortality rates. The National Institutes of Health estimated that the cost of all cancers in the United States totaled \$206.3 billion in 2006, with direct medical costs contributing \$78.2 billion, indirect morbidity costs (cost of lost productivity due to illness) contributing \$17.9 billion, and indirect mortality costs (cost of lost productivity due to premature death) contributing \$110.2 billion.<sup>16</sup>

Indirect costs are also significant in cervical cancer and are likely several times greater than direct costs.<sup>14</sup> Insinga's study of lost productivity due to premature death from cervical cancer determined that more than 130,000 women would likely have been alive in the year 2000 had they not died prematurely from cervical cancer.<sup>17</sup> He found that more than 75% of women who received a diagnosis of cervical cancer died before 60 years of age and 25% died before 40 years of age.<sup>17</sup> Using workforce participation data from 2000, Insinga estimated that 29% of the women would have been active in the workforce that year. Based on the projected annual earnings for these women, the study estimated a loss of \$1.3 billion (in 2000 US dollars).<sup>17</sup> This was significantly more than the estimated annual direct medical costs of \$300 to \$400 million (in 2004 US dollars) associated with cervical cancer. This study and others have estimated that the indirect costs of cervical cancer constitute more than three fourths of the overall economic burden of the disease.<sup>17,18</sup>

A study by Max et al used California hospital discharge information from 1997 to estimate direct and indirect costs for cervical and other gynecologic cancers that were either primary or secondary diagnoses.<sup>18</sup> There were 452 cervical cancer deaths that year, and because cervical cancer often occurs in younger women, it was estimated that 28.7 life-years were lost per death, resulting in approximately 12,989 total life-years lost.<sup>18</sup> The total estimated

loss of future earnings (in 1998 US dollars) was determined to be \$158 million discounted at 3%, or a loss of \$350,839 per cervical cancer death. The study also found that indirect costs were twice the direct costs.<sup>18</sup>

Indirect costs, with a primary focus on lost productivity and future earnings, have not been studied and documented as extensively as direct costs. This may be partly because of the qualitative nature of indirect costs and the overall lower level of interest in these costs in managed care, except to employers and epidemiologists. Reported cost estimates are likely underestimated, because the existing data sets have not fully considered costs related to lost work or leisure time resulting from follow-up secondary prevention, disease-associated morbidity, and cancer treatment. Despite this apparent underestimation, the impact of indirect costs relative to cervical cancer remains significant to society and particularly to employers within the managed care process.

### Conclusion

Oncogenic HPV infection has a profound impact on managed care because of its growing prevalence in the US population (owing to the ease with which it is transmitted) and the resultant rates of morbidity and mortality, which are significant. HPV-related cervical cancer and cervical dysplasias are associated with the highest direct and indirect costs of all HPV-related diseases. Combined, these conditions cost an estimated \$5 billion annually (in 2006 US dollars), with cervical cancer and cervical dysplasias related to oncogenic HPV infection estimated to account for direct medical costs of up to \$4.6 billion.<sup>1,12</sup> This includes an estimated \$2.4 billion for routine cervical screening and an estimated \$339 million resulting from false-positive Pap test results.<sup>1</sup> In addition to direct costs, indirect costs related to lost productivity and future earnings, which are likely underestimated, have been determined to be more than 2 to 3 times the direct medical costs.<sup>17,18</sup> There are also significant psychological and emotional burdens—some of which can last a lifetime—placed on women who receive abnormal test results or a diagnosis of oncogenic HPV infection or cervical cancer.<sup>12</sup>

The extensive screening and prevention programs in the United States have contributed signif-

icantly to the decreasing mortality rates associated with cervical disease, but they also account for more than two thirds of the total spent on cervical disease; only 10% is spent on managing invasive disease.<sup>1</sup> Although secondary prevention methods have been successful, screening is not entirely reliable, with Pap tests detecting only 60% to 90% of abnormal cytology, according to some studies.<sup>19,20</sup> Even when abnormal cytology is identified, 13% of invasive cervical cancer cases have been attributed to incomplete follow-up of screening results.<sup>21</sup> Finally, screening cannot be effective when it is not conducted, and a majority of cervical cancers are diagnosed in women who have not undergone a Pap test in 3 years.

An adjunctive intervention to screening that reduces the rates of HPV infections, abnormal Pap test results, and invasive cervical cancer would have a significant positive impact on women's health and the resources dedicated to care. Reducing the diagnoses of HPV-related cervical cancer and cervical dysplasias should decrease the financial and emotional burdens of these diseases.

Secondary prevention methods can do only so much to capture existing disease. The use of effective HPV vaccines as primary protection against cervical cancer can further reduce the morbidity and mortality rates associated with HPV-induced cervical disease. The US Department of Health and Human Services recognizes the potential of HPV vaccines as part of a 2-tiered approach to preventing cervical cancer and cervical dysplasia and has recommended further development of such interventions.<sup>22</sup> Early data from HPV vaccine clinical trials are promising. HPV vaccination should confer primary protection to women against cervical cancer and the development of precursor lesions, conditions that have proven to be emotionally, clinically, and financially challenging.

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