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## Update on prevention and screening of cervical cancer

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## Abstract

Cervical cancer is the third most common cause of cancer in women in the world. During the past few decades tremendous strides have been made toward decreasing the incidence and mortality of cervical cancer with the implementation of various prevention and screening strategies. The causative agent linked to cervical cancer development and its precursors is the human papillomavirus (HPV). Prevention and screening measures for cervical cancer are paramount because the ability to identify and treat the illness at its premature stage often disrupts the process of neoplasia. Cervical carcinogenesis can be the result of infections from multiple high-risk HPV types that act synergistically. This imposes a level of complexity to identifying and vaccinating against the actual causative agent. Additionally, most HPV infections spontaneously clear. Therefore, screening strategies should optimally weigh the benefits and risks of screening to avoid the discovery and needless treatment of transient HPV infections.

This article provides an update of the preventative and screening methods for cervical cancer, mainly HPV vaccination, screening with Pap smear cytology, and HPV testing. It also provides a discussion of the newest United States 2012 guidelines for cervical cancer screening, which changed the age to begin and end screening and lengthened the screening intervals.

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**Key words:** Cervical cancer; Cancer screening; Pap smear; Human papillomavirus; Papillomavirus vaccines

**Core tip:** Screening is the best method to prevent cervical cancer. Screening strategies should weigh the benefits and risks of screening to avoid discovery and needless treatment of transient human papillomavirus (HPV) infections. Current United States guidelines recommend Pap smear screening with conventional or liquid-based method no frequent than every 3 years, or every 5 years in women greater than age of 30 if done in conjunction with HPV testing. Screening is not recommend in females younger than 21 years, regardless of age at initiation of sex. In this population, options for prevention include HPV vaccination and decreasing other risk factors associated with HPV infection.

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## INTRODUCTION

The World Health Organization estimates that yearly, about 530000 women worldwide are identified with cervical cancer and 275000 women die from the disease<sup>[1]</sup>. Cervical cancer is heralded as being the third most common cause of cancer among women in the world and

the second most common form of cancer in women in the developing world<sup>[2]</sup>. Cervical cancer is responsible for the largest cause of mortality in women due to cancer in most developing countries.

There has been a large decline in the incidence and death rate of cervical cancer in industrialized countries observed during the past few decades. This unfortunately, has not been mirrored by a similar decline in developing nations. An example of this is illustrated by the 70% decrease in mortality caused by cervical cancer in the United States from 1955 to 1992. Each year this initial decline in death caused by cervical cancer has been sustained at a rate of a 3% decrease in the incidence of cervical cancer<sup>[2]</sup>. Similarly, in the United Kingdom there has been a 70% decline in the mortality caused by cervical cancer recorded in 2008 than was reported 30 years prior<sup>[2]</sup>. In industrialized nations the age-adjusted incidence of cervical cancer is 10 out of 100000 per year; however in developing nations the incidence of the disease can be as high as 40 out of 100000. By 2030, it is expected that cervical cancer will be responsible for the death of 474000 women annually with over 95% of these deaths anticipated to occur in low- and middle-income countries (LMICs)<sup>[3]</sup>.

### HPV infection and cervical cancer

Infection with HPV is the main causative agent in cervical cancer. The latest estimation of the number of genotypes of HPV was 200 with 18 genotypes that are directly related to cervical cancer<sup>[4,5]</sup>. The fifteen HPV types that have a strong oncogenic potential include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. These high-risk HPV types account for 95% of all cervical cancer.

It has been found that greater than one HPV type can exist in pre-invasive and invasive cervical cancer<sup>[6]</sup>. This imposes a level of complexity in identifying which one is the actual causative agent, with various genotypes depending on geographical regions. While high-risk HPV 16 and 18 are accountable for around 90% of all cervical cancer<sup>[7]</sup>, there is greater than average presence of subtypes 31 and 45 detected in the developing world<sup>[8]</sup>. There is also a prominent presence of HPV 58 associated with pre-invasive lesions in women in various countries, including Thailand, Uganda, Zambia and Cameroon<sup>[9-12]</sup>.

The most carcinogenic HPV genotype is HPV 16, which mostly causes squamous cell carcinoma. HPV 18 mostly causes adenocarcinoma, a cancer that is less frequently found but more aggressive, resulting from the endocervical glandular<sup>[13]</sup>. However, cervical carcinogenesis may arise from infections with many high-risk types that act synergistically<sup>[14]</sup>. The Bethesda classification encompasses the biological behavior of cervical squamous intraepithelial lesions (SILS)<sup>[8]</sup>. The classification system partitions abnormal squamous epithelial cells into four categories: (1) atypical squamous cells of undetermined significance (ASCUS); (2) low grade squamous intraepithelial lesions (LSILS), including light dysplasia/cervical intraepithelial neoplasia (CIN) 1 in addition to HPV associated cell changes; (3) high-grade squamous intraepithelial le-

sions (HSIL), encompassing moderate dysplasia/CIN 2, severe dysplasia, and carcinoma *in situ*/CIN 3; and (4) squamous cell carcinoma<sup>[8]</sup>. Almost 90% of infections with HPV clear on its own within 1-2 years<sup>[15]</sup>. High-grade cervical intraepithelial lesions that are classified as CIN 2 have a 40% chance of regression. High-grade cervical intraepithelial lesions that do not regress are categorized as CIN 3. These lesions have a 30% probability of progression to invasive cervical cancer<sup>[16]</sup>. HPV 16 is the most persistent infection and the type that is most likely to progress to CIN 3, carcinoma *in situ*, and invasive cervical cancer. HPV negative cervical cancer is extremely rare, but it has been found. This form of cervical cancer is believed to be due to an artifact caused by limitations in the current detection methods or perhaps due to the loss of HPV DNA during the progression to cancer.

### Risk factors for cervical cancer

Sexually transmitted infection with HPV is the strongest risk factor for development of cervical cancer. There are multiple risk factors that have been connected with the acquisition of HPV infection and cervical cancer (Table 1). HPV acquisition is most dependent on genital contact. This prominent risk increases with higher number of sexual partners of a woman or her partner<sup>[17-19]</sup>. Other sexual and reproductive risk factors associated with HPV infection and cervical cancer include: initiation of sexual activity at an early age ( $\leq 18$  years), earlier age at first full-term pregnancy ( $< 18$  years), high parity (4 or greater vaginal deliveries), use of combined hormonal oral contraceptives for longer than 5 years, and a history of other sexually transmitted infections [*e.g.*, chlamydia, human immunodeficiency virus (HIV), herpes simplex 2]<sup>[18,19]</sup>. The use of tobacco, both current and past, increases the risk of squamous cell cervical carcinoma, and the risk rises with quantity of cigarettes smoked per day and number of years smoked<sup>[19]</sup>. Infection with HIV is strongly associated with incidence and persistence of HPV infection, and advancement to invasive cervical cancer from squamous intraepithelial lesions<sup>[19]</sup>. In fact, cervical cancer is one of the acquired immunodeficiency syndrome (AIDS)-defining illness, *i.e.*, a person with HIV who develops cervical cancer is considered to have AIDS. The acquisition of HPV is most dependent on contact with the genital skin and condom use is associated with reduced cervical cancer risk<sup>[19]</sup>. However, condom use is only 70% effective in averting the transmission of HPV since there is remaining contact with genital skin that is not covered by the surface of the condom<sup>[17]</sup>. In summary, counseling for tobacco cessation, delaying initiation of sexual intercourse, using condoms, and decreasing number of sexual partners may prevent HPV infection and help to reduce the risk of cervical cancer.

## CERVICAL CANCER PREVENTION WITH HPV VACCINATION

Another potential way to prevent cervical cancer is the

**Table 1 Cervical cancer risk factors**

Cervical cancer risk factors <sup>[17-19]</sup>
Genital Infection with high risk human papillomavirus
HIV infection
Smoking
Younger age at first sexual intercourse
Greater number of sexual partners
Oral contraceptives use greater than 5 yr
Having 4 or greater full-term pregnancies
History of sexual transmitted diseases

HIV: Human immunodeficiency virus.

use of HPV vaccination to prevent high risk HPV infection and subsequent cervical carcinogenesis. The Food and Drug Administration (FDA) approved in 2006, Gardasil, a recombinant quadrivalent HPV vaccine. This vaccine has the capability of preventing infection with HPV 16 and 18 in addition to HPV 6 and 11, and it is targeted for use in females 9-26 years of age<sup>[20]</sup>. It has been marketed as having the ability to prevent genital warts as well as cervical cancer when given in three vaccinations, at months 0, 1 to 2, and 6<sup>[21]</sup>. Gardasil also has the capability to convey protection against vulvar, vaginal cancer and intraepithelial neoplasia, and recently, for the deterrence of genital warts in males age 9-26 years<sup>[6]</sup>. Short to medium clinical studies show the capability of Gardasil to protective against HPV-16 and 18 infections and its associated precancerous lesions for up to 5 years post vaccination<sup>[6,8,13]</sup>.

In 2008, a second vaccine, Cervarix, the HPV bivalent vaccine targeting HPV 16 and 18 was approved<sup>[22]</sup>. Cervarix is indicated for use in females aged 10 to 25 years when given in three vaccinations at months 0, 1 to 2, and 6<sup>[23]</sup>. Cervarix is effective against anogenital warts caused by HPV, precancerous lesions, and cervical cancer<sup>[6]</sup>. Short to medium clinical studies show Cervarix conveys protection against HPV-16/18 and its associated precancerous lesions for 6.4 years post vaccination<sup>[2,10,15,20]</sup>.

The two HPV vaccines, Gardasil and Cervarix, are currently approved in over 100 countries. In their individual trials, the efficacy of Cervarix in protecting against cervical cytologic abnormalities in HPV-naïve women is slightly higher than Gardasil<sup>[19]</sup>. Cervarix also seems to have higher cross-protection against other nonvaccine HPV types, as evidenced by its higher reduction in excisional treatments for CIN 2/3 disease compared to Gardasil, and its efficacy in decreasing incidence of genital warts caused by HPV 6, 11, and 74<sup>[19]</sup>. However, clinically significant differences in efficacy of Gardasil *vs* Cervarix is difficult to discern and will not be apparent for many years. Researchers believe that the differences will be revealed with longer-term evaluations of women that were vaccinated in countries with population-based registries that can track HPV associated cervical lesions<sup>[8]</sup>.

There are a cluster of symptoms that have been reported most frequently in correlation to administration

of the HPV vaccines including pain where injected (78%), ecchymosis (17%), fainting (15%), and swelling (14%). These side effects have been reported most commonly in younger than older girls<sup>[24]</sup>.

Routine HPV vaccination of girls is recommended by the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) at 11 to 12 years of age with catch-up vaccinations at 13 to 26 years of age<sup>[25]</sup> (Table 2). However, the American Cancer Society has not found enough research evidence to recommend for or against routine vaccination of females age 19 to 26 years<sup>[24]</sup>. Young women are the targeted group because immunological response is greatest in girls aged 10-15 years, and the vaccine has greatest efficacy in girls who haven’t initiated sex<sup>[26]</sup>. Estimations have been made that only 7% of students in United States high schools report having started sexual intercourse prior to 13 years of age<sup>[26]</sup>. In the developing world there is a much variation in the prevalence of virginity and the age which women marry. Therefore, international vaccination programs may have to change according to their country’s conditions and traditions<sup>[27]</sup>.

**Barriers to implementation of HPV vaccine**

The acquisition of immunity of the entire population or herd immunity has been met by a great deal of challenges. Advocates for the vaccine estimate that approximately 70%-80% of girls that are pre-pubertal are required to be vaccinated to obtain herd immunity. This level of immunity will be hard to reach in light of the fact that many conservatives in the US have described the drug as “the promiscuity vaccine” and have imposed their fears that inoculating preteen girls will disrupt their message of abstinence from pre-marital sexual intercourse *via* what they have called the “disinhibition effects”<sup>[28]</sup>. All of this political rhetoric has resulted in a shift in public opinion of the vaccine and resulted in a decline in the percentages of parents that are in favor of the vaccine. Interestingly, the intention to vaccinate with HPV is greatest when the vaccine is depicted that it is free or cheaply available and that it prevents cancer, rather than preventing an infection that is sexually transmitted<sup>[25]</sup>. Studies show that there are still realist barriers in place as it pertains to the cost of the vaccine as well as the stigma that is attached to it<sup>[27]</sup>.

Advocates for the HPV vaccination also believe that herd immunity will only authentically be obtained when there is the existence of a gender-inclusive vaccination policy<sup>[28]</sup>. There is a belief that men play a pivotal role as carriers of HPV. However, there has been a limited amount of clinical trials that have been carried out on boys as it pertains to HPV vaccinations. This fact is even reflected in the lack of attention given to administering HPV vaccines to boys and men in United States newspapers<sup>[29]</sup>. Positive strides have been made with regards to boys and men immunization when the ACIP approved the non-routine vaccination of Gardasil in boys age nine to 18 years for the purpose of preventing genital warts<sup>[29]</sup>. While it is known that males represent a reservoir for fe-

**Table 2 Recommendations for human papillomavirus vaccination by the Advisory Committee on Immunization Practices**

Population	Recommendation for HPV vaccination
Females 11-12 yr of age	Routine vaccination with 3 doses at 0, 1-2, and 6 mo of either HPV2 or HPV4. Can be initiated as early as age 9 and be given up to age 26
Females 13-26 yr of age	Catch up immunization with 3 doses at 0, 1-2, and 6 mo of either HPV2 or HPV4
Males age 11-12 yr	Routine vaccination with HPV4 with 3 doses at 0, 1-2, and 6 mo. Can be initiated as young as age 9 and be given up to age 26
Female or males with inadequate dose of HPV vaccine	Minimum time between 1 <sup>st</sup> and 2 <sup>nd</sup> vaccine doses is 1 mo. Minimum time between the 2 <sup>nd</sup> and 3 <sup>rd</sup> vaccine doses is 3 mo. Insufficient receipt of HPV vaccine due to shorter than the recommended dosing interval should be re-administered
Females or males with interrupted vaccine schedule	HPV vaccination does not need to be restarted. The 2 <sup>nd</sup> dose should be administered as quick as possible if delayed after the 1st dose. The 2 <sup>nd</sup> and 3 <sup>rd</sup> dose should be separated by 3 mo. If just the 3 <sup>rd</sup> dose is late, it should be given as soon as possible

HPV: Human papillomavirus vaccine; HPV2: Bivalent human papillomavirus vaccine (Cervarix); HPV4: Quadrivalent human papillomavirus vaccine (Gardasil).

male HPV infections, HPV vaccination in boys is controversial because there is no proof that it is cost-effective<sup>[29]</sup>.

While the controversy over the cost-effectiveness of the vaccine in males as well as the debate surrounding the use of the vaccine in young girls continue, some question the true effectiveness of the HPV vaccine. The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) trials that validated the effectiveness of the vaccine were only conducted over a three-year timeline<sup>[21]</sup>. However, the average time from carcinogenic HPV infection to invasive cervical cancer, if it happens, is at least 25-30 years<sup>[22,30]</sup>. Furthermore, it takes approximately five to seven years from acquisition of HPV infection and the first incidence of a pre-invasive cervical lesion<sup>[22]</sup>. As a result of this reasoning, some argue that to declare that the vaccine averted the occurrence of cervical lesions after only a few years of follow-up has the potential to be misleading.

Another factor that concerns the international community is the presence of serotypes that are not targeted by the two HPV vaccines<sup>[31,32]</sup>. For example, the quadrivalent vaccine prevents infection from HPV 16, 18, 6 and 11, and the bivalent vaccine targets HPV 16 and 18, however, there are other genotypes of HPV that are prevalent in other geographical regions. Consequently, a daunting question is imposed on the effectiveness of the current vaccines in these other regions.

## CERVICAL CANCER SCREENING

The ultimate objective of cervical cancer screening is to find high-grade cancer precursor lesions and early asymptomatic invasive cervical cancer, while avoiding the discovery and needless treatment of fleeting HPV infection and its resultant benign lesions. Since the majority of HPV infections and many CIN 1 and CIN 2 cases are transient, there is a large margin for harm that is associated with discovering these fleeting lesions, including mental stress, physical discomfort incurred from extra diagnostic and treatment measures (*e.g.*, vaginal pain, bleeding, infection), and a higher risk of maternity complications such as preterm delivery after treatment<sup>[33,34]</sup>.

The systemic screening with the Papanicolaou cy-

tological test (Pap smear) to find pre-invasive cervical lesions and early stage cancer has drastically reduced the incidence and death from cervical cancer in the United States and other industrialized nations<sup>[34]</sup>. However, cervical cancer still produces much morbidity and mortality in certain sub-populations. In the United States, approximately one-half of cervical cancer is diagnosed in women who were never screened. Groups of the population that participate least frequently in Pap smear include: women who are less educated, older, uninsured, or homeless; migrant workers who face language barriers; and lesbians<sup>[24]</sup>. The segment of the United States population at highest risk for cervical cancer is Hispanic and African American women. Fortunately, these populations have benefited from community-based awareness raising programs, which have successfully resulted in a decline in their prevalence of cervical cancer<sup>[35]</sup>. It is then practical to reason that programs similar to the ones implemented on Hispanic and African-American women should be applied to the various groups of the population where the women are at greater risk to having cervical cancer due to their lack of compliance with Pap smear screening.

### Cervical cytology tests

There are two forms of Pap smears, conventional and liquid-based cytology. In the conventional method cells are obtained from the neck of the cervix and then the cells are spread on a glass slide. In the liquid-based cytology method, the cells are obtained from the neck of the cervix, but instead of being spread on a glass slide, they are placed in a small glass vial that contains preserving fluid. There has been much debate with regards to which form is superior. Current evidence indicates that no clinically important differences in sensitivity or specificity exists when comparing liquid-based and conventional cytology<sup>[36]</sup>. The United States Preventive Services Task Force (USPSTF) considers both of these methods to be of substantial net benefit when they are administered in the appropriate age groups at the recommended interval<sup>[37]</sup>.

### HPV testing

Although the Pap test has proven to be a greatly effec-

tive tool for screening in countries that have the capacity to implement it to the majority of its population, one problem with the test is its high rate of false positive cytology<sup>[38]</sup>. The higher understanding of the correlation between HPV and cervical cancer led to the development of molecular tests for HPV with greater sensitivity (approximately 90 percent)<sup>[39]</sup>. However, it has slightly reduced specificity for CIN2 and CIN3 when compared with cytology. The currently available DNA test detects only the high-risk HPV types, and has greater reproducibility than cytology. The HPV test is a solution hybridization that has the capacity to amplify the DNA signal in the assays of the 13 HPV high-risk types<sup>[14]</sup>. The HPV test should be performed only in women age 30 years or more because women less than 30 years have a high prevalence of transient infection and a low prevalence of underlying high-grade lesions<sup>[37]</sup>. Therefore, HPV DNA testing in women under the age of 30 can lead to unneeded evaluation and overtreatment<sup>[37]</sup>.

At the present time HPV DNA testing has the highest sensitivity, which can additionally be used with Pap smears (co-testing) for optimizing diagnosis of high-grade cervical intraepithelial neoplasia<sup>[39]</sup>. In women with mild or borderline abnormal Pap results, a Pap-plus-HPV test may be better, since a negative HPV DNA test has the potential to assure women that their Pap smear result is probably untrue; whereas treatment for a positive HPV DNA test may begin quicker in these women due to the high sensitivity of this test<sup>[40]</sup>.

### Visual inspection with acetic acid

Low-and-middle-income countries (LMICs) are faced with a lack of critical resources for health in general and often an even larger deficit for preventative health initiatives for women. To combat this, LMICs pursue screening options that work within the various societal confounds faced by women in their countries. The majority of these LMICs do not have the current capacity to sustain cytology-based cervical cancer prevention programs<sup>[41]</sup>. In these societies, the Pap test is hindered by numerous operational factors that inhibit quality, including the follow-up challenges of multiple visits for screening and later post-diagnosis therapy, inefficient recall and referral systems, inadequate resources for screening and treatment, and competing priorities in the healthcare systems<sup>[41]</sup>. A viable alternative to the Pap test has been developed due its low cost and ability to “see-and-treat” in one visit. This screening method, known as visual inspection with acetic acid (VIA), partnered with cryotherapy-based treatment of VIA-positive lesions is a testing method that has been readily mastered by non-physician providers and has been extensively studied as a viable alternative to the Pap smear<sup>[41,42]</sup>. A method of screening that is gaining increasing popularity in LMICs is the combination of VIA-based “see-and-treat” platforms with HPV DNA testing, given that they have the benefit of same-visit benefit of triage by VIA-based screening<sup>[43-45]</sup>. This opportunity is made possible with the

ongoing development of low-cost, rapid molecular-assay technologies for HPV that may function optimally in the field<sup>[46,47]</sup>.

## CURRENT GUIDELINES FOR CERVICAL CANCER SCREENING

In the United States, there has recently been a shift in the way that screening for cervical cancer is being conducted with recognition that yearly screening was unnecessary and caused higher rate of harms. This is due to greater understanding of the pathological development of cervical cancer and the discovery of the HPV DNA test and HPV vaccines that have occurred in the last decade. Consequently, screening guidelines have evolved rapidly, and many of the organizations that develop screening guidelines now agree on the screening recommendations<sup>[27,48,49]</sup>. The American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society of Clinical Pathology (ASCP) all tasked expert panels within the past five years to review the available evidence on cervical cancer screening and jointly produce a new cervical cancer screening guideline. At the same time, the United States Preventive Services Task Force (USPSTF) developed an updated systematic review of cervical cancer screening. On March 14, 2012, The ACS/ASCCP/ASCP group<sup>[35]</sup> and the USPSTF<sup>[36]</sup> released their updated guidelines. The American Congress of Obstetrics and Gynecologist (ACOG) issued their updated guidelines for cervical cancer screening shortly thereafter in November 2012<sup>[50]</sup>. The consensus of recommendations made by these organizations, as it pertains to cervical cancer screening, are for the general population only. The guidelines are not for women that are at a high risk, as they may need more frequent screenings, including women with a history of cervical cancer, who are immunocompromised, or were exposed in utero to diethylstilbestrol<sup>[50]</sup>.

Table 3 presents the current guidelines for specific age groups. These differ from previous recommendations most notably in when to begin screening and the screening intervals. Women before the age of 21 years should not have Pap smears, irrespective of the age when they initiated sexual activity<sup>[37,48,49]</sup>. The previous guidelines by the ACS in 2002 and 2003 stated that Pap smears should start 3 years following the initiation of sexual intercourse<sup>[37,51]</sup>. There has been a call for lengthening the screening intervals in two of the age classifications. The updated ACS/ASCCP/ASCP and ACOG guidelines<sup>[51,52]</sup> have increased the time between Pap smears to 3 years in females between ages 21 to 29. Their previous guidelines recommended screening be done every 2 years. The reason behind this change in the guidelines is because 2-3 year screening of women before age 30 carry similar predicted lifetime risk of cervical cancer mortality (0.05 per 1000 women); however screening women every 2 years increases the risk of colposcopies by 40% compared with screening every 3 years<sup>[49]</sup>. Hence, 3 year screening in

**Table 3 Comparison of cervical cancer screening guidelines**

Population	Current Guidelines ACS/ACOG/USPSTF 2012	Prior ACS guideline 2002/2003	Prior ACOG guideline 2009	Prior USPSTF guideline 2003
Females younger than 21 yr of age	Begin screening at age 21	Begin 3 yr following the onset of vaginal intercourse, but no later than 21 yr	Begin 3 yr following the onset of vaginal intercourse, but no later than 21 yr	Begin within 3 yr of onset of sexual activity or age 21, whichever is earliest
Females age 21–29 yr	Conventional Pap or liquid based cytology alone every 3 yr	Conventional Pap: Annually; every 2–3 yr for females $\geq$ 30 with 3 negative cytology tests Liquid-based cytology: Every 2 yr; every 2–3 yr for females $\geq$ 30 yr with 3 negative cytology tests If HPV testing used: Every 3 yr if HPV negative and cytology negative	Cytology every 2 yr	Conventional Pap: At least every 3 yr Liquid-based cytology: Insufficient evidence If HPV testing used: Insufficient evidence
Females age 30–65 yr	HPV and Pap smear co-testing every 5 yr or Pap smear alone every 3 yr. Do not use HPV testing alone.		HPV and cytology co-testing every 3 yr	
Women older than 65	Stop screening if adequate prior negative screening result and women not at high risk	Stop screening in Women $\geq$ 70 yr with 3 or more recent, consecutive negative tests and no abnormal tests in previous 10 yr	Stop between 65 and 70 yr of age after > 3 consecutive negative cytology tests over the past 10 yr	No screening if adequate prior negative screening result and women not at high risk
Women after hysterectomy	No screening if removal of cervix and no prior high grade pre-cancer or cervical cancer	Discontinue if hysterectomy for benign reasons and no previous high-grade CIN	Stop screening	Discontinue if hysterectomy done for benign reasons
Women who were immunized with HPV	Same as non-immunized women	No vaccines recommended for use at this time period	Same as non-immunized women	No vaccines recommended for use at this time period

ACS: American Cancer Society; ACOG: American Congress of Obstetricians and Gynecologists; USPSTF: United States Preventive Services Task Force; HPV: Human papillomavirus; CIN: cervical intraepithelial neoplasia.

women younger than age 30 years has the optimal benefit to risk ratio. In women 30 to 65 years of age, screening can be done every 5 years if the woman's result on co-testing with Pap smear and HPV testing are negative, since co-testing increases the sensitivity of screening, and co-testing every 5 years results in fewer colposcopies and comparable cancer risk than Pap smear screening every 3 years<sup>[52,53]</sup>. Cytology testing only at 3-year intervals is also satisfactory in this patient population. The new guidelines also recommend a decrease in the age that screening is stopped, from 70 to 65 years<sup>[49,50,54]</sup>. The reason for this is that studies show in women age 65 or older, new high-risk HPV infection is associated with a extremely low absolute risk of HPV persistence and progression to CIN3<sup>[55,56]</sup>.

There are some special circumstances that require specific recommendations in the screening guidelines. The new guidelines maintain previous recommendations to not screen women that have received hysterectomies with excision of the cervix for a benign cause and who do not have prior history of cervical cytology higher than CIN2<sup>[37,48,49]</sup>. This recommendation has been made in part based on evidence produced by a large study of 5330 screening Pap smears in women with previous hysterectomy where there was just one person found with dysplasia and none with cervical cancer<sup>[56]</sup>. Another unique circumstance that has arisen since 2006 was the advent

of the HPV vaccine. Current guidelines recommend the same screening strategy in individuals that have received the vaccine as in individuals that have not had the vaccine because it will be another decade or more before modeling studies predicting the effectiveness of the vaccine will be available<sup>[57]</sup>. The guidelines also address the situation when women have a negative Pap smear but a positive HPV test. The ACS/ASCCP/ASCP and ACOG recommend genotyping of HPV 16/18 and if positive, immediate colposcopy<sup>[49]</sup>. However, evidence for HPV 16/18 genotyping is sparse; therefore, an acceptable alternative option is to perform the combined HPV and cytology testing again within 12 mo<sup>[49,58]</sup>. These recommendations are based on results found in large cohort studies showing that the risk of CIN 3 approximates 10% over 1 to 4 years when a woman's test is evident for HPV 16, and over 2 to 5 years if the woman's test shows HPV 18<sup>[59,60]</sup>.

## DISCUSSION AND FUTURE PERSPECTIVE ON CERVICAL CANCER PREVENTION AND SCREENING

With the advent of the HPV vaccine and the limitless screening possibilities that have been afforded by the growing understanding of HPV and the role that it plays in the evolution of cervical cancer, there is a real possibil-

ity that cervical cancer can be eliminated in the future. However, for that vision to become a reality there are numerous complexities that have to be resolved with regards to prevention as well as to screening for cervical cancer. The innovative strides that have been made at the present time must be met by global efforts that are tailored to various societal confines.

In the United States there has been a push by health care providers for immunization with HPV vaccine routinely in young women. This effort has not only been met by opposition created from those challenging the morality and questioning the effectiveness of the vaccine; it has also been met by exclusion of male counterparts in the dissemination of this vaccine, as well as the ever present lack of access of certain populations to adequate health care. Individuals that are at higher risk of acquiring cervical cancer are those that demonstrate less knowledge of HPV and the HPV vaccine. Therefore, educational outreach and program funding is needed that are targeted at reaching the subgroups of the population with low health care literacy and who are at risk of succumbing to the morbidity and mortality of this preventable cancer.

The call to local and governmental officials to enhance the educational outreach and program funding as a means to decrease the incidence of morbidity and deaths due to cervical cancer is also at the frontline of the dialogue in LMICs. Immunization of women with HPV vaccine to potentially prevent cervical cancer in these regions may take a back seat to other health care issues in light of the cost and the unique blend of genotypes that are present based on the geographical region. Fortunately, officials in these regions are becoming more knowledgeable of the advantages of implementing innovative cervical cancer see-and-treat programs. There is a continued need for industrialized nations to lend aid to these countries. This aid should not only be sent in the form of the monetary contributions that have been made by vaccine manufactures; they should continue sending aid via providing the service of individuals that can train their non-physician workforce who do a great deal to treat the masses of women in their countries.

In both LMICs and developed countries, the advent of HPV DNA testing has had a tremendous impact on the way that screening for cervical cancer is conducted. Affordable versions of this test are being developed, non-physician providers can perform it independently, and the results can be obtained the same day. More research needs to be done to see if testing with this technology should be conducted as the primary testing method, especially in hard to reach populations, since compared to cytology, it offers extended safety after a negative result. Some experts argue that because testing for HPV has greater sensitivity than Pap smear, while Pap smear screening has greater specificity, HPV testing should be performed initially and then obtain Pap smear screening for patients testing positive for HPV. The potential advantage to this was seen in a Canadian trial that found that HPV testing followed by Pap smear caused lower re-

ferrals for colposcopy than did either alone (1.1% *vs* 2.9% with only Pap smear or 6.1% with just HPV testing)<sup>[59]</sup>.

The greatest effect on mortality rates from cervical cancer is on women that are unscreened or under screened. There is a huge need to continue with the innovative strides that have been made to overcome the health care barriers crippling this population. If this population is able to benefit from low-cost screening and vaccinations subsidized by the government and continued efforts that are being made possible by the growing dialogue surrounding cervical cancer, it is possible that women in future generations will no longer succumb to cancer of the cervix.

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