Preventing Cervical Cancer: Primary and Secondary Measures

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INTRODUCTION

Worldwide, cervical cancer is the second most frequent cancer and fifth most frequent cause of death from cancer among women, with an estimated 493,000 new cases and 273,000 deaths in 2002.[1] Eighty-three percent of new cases and 85% of deaths from cervical cancer occur in developing countries. In South-east Asia, the age-standardized incidence ranges from about 10 per 100,000 women in Hong Kong and Singapore to about 20 per 100,000 women in Malaysia, The Philippines, Thailand and Vietnam.[2,3] In China, a systematic, national-level cancer registry does not exist, but sample surveys showed that in 2002, the incidence rate of cervical cancer ranged from 2.4 per 100,000 women in Jiashan to 4.6 per 100,000 women in Guangzhou. However, specific areas have notably high incidences of cervical cancer, such as YangCheng, ShanXi, with an age-adjusted estimated incidence rate of 81 per 100,000 women between 1998 and 2002.[4] Unlike most other cancers, cervical cancer is highly preventable when precursor lesions are detected and treated before they develop into cancer. The prevention of cervical cancer includes primary, secondary and tertiary prevention. Primary

Most infections of the human papillomavirus in young women are transient.

prevention can be achieved by avoiding exposure to risk factors and causative agents such as the human papillomavirus (HPV), or by vaccination; secondary prevention means detecting the precancerous disease through screening, and providing treatment; and tertiary prevention includes measures to reduce recurrence or progression of an invasive disease, or palliative measures. In this review, we will focus on primary and secondary prevention.

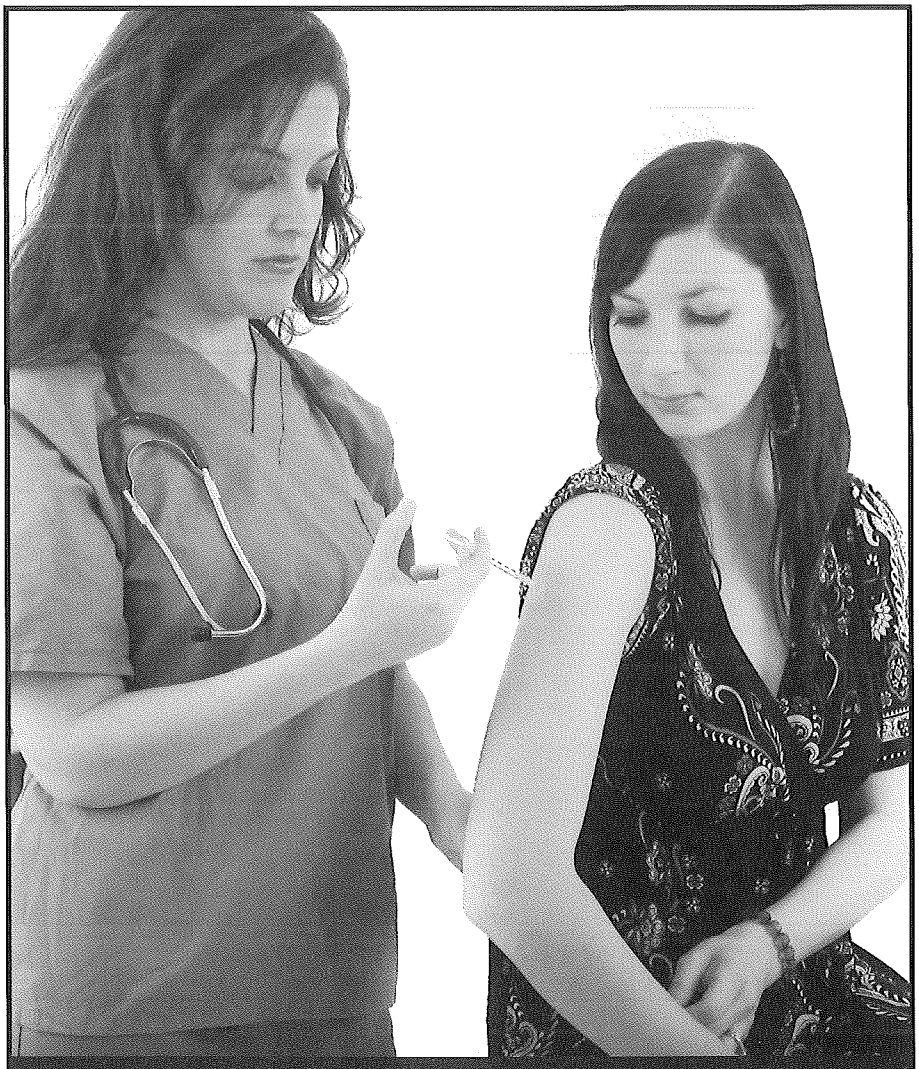
PRIMARY PREVENTION

Reducing Exposure to Risk Factors Associated with HPV Infection

The causal role of persistent infection associated with high-risk HPV types in cervical carcinogenesis has now been clearly established. Reducing HPV infection is one of the most important preventive measures in reducing cervical cancer. This can be achieved by reducing exposure to or vaccinating against the virus. HPV infection is mainly transmitted by sexual contact; therefore, abstinence from sexual activity or mutual monogamy will reduce the risk of exposure to the virus. Condoms can provide about 70% protection against HPV when used at all times.[5]

Factors associated with HPV persistence include immune suppression, cigarette smoking, multiparity, early age of first sexual intercourse, long-term use of hormonal contraceptives and infection with sexually transmitted diseases (eg, *Chlamydia trachomatis* and Herpes simplex virus type 2).[6–13] It had been shown that ever and current smoking increases the risk of cervical cancer among HPV-positive women. Among cases of squamous cell carcinoma, an excess risk was observed for current smokers (odds ratio [OR], 2.30; 95% confidence interval [CI], 1.31–4.04) and ex-smokers (OR, 1.80; 95% CI, 0.95–3.44).[8] Among HPV-infected women, those who had seven or more full-term pregnancies have approximately four times the risk of squamous cell cancer compared with nulliparous women, and two to three times the risk compared with women who had one or two full-term pregnancies.[9] A multicentre case-control study showed that among HPV-infected women, those who used oral contraceptives for 5 to 9 years have approximately three times the incidence of invasive cancer, and those who used them for 10 years or longer have approximately four times the risk.[10]

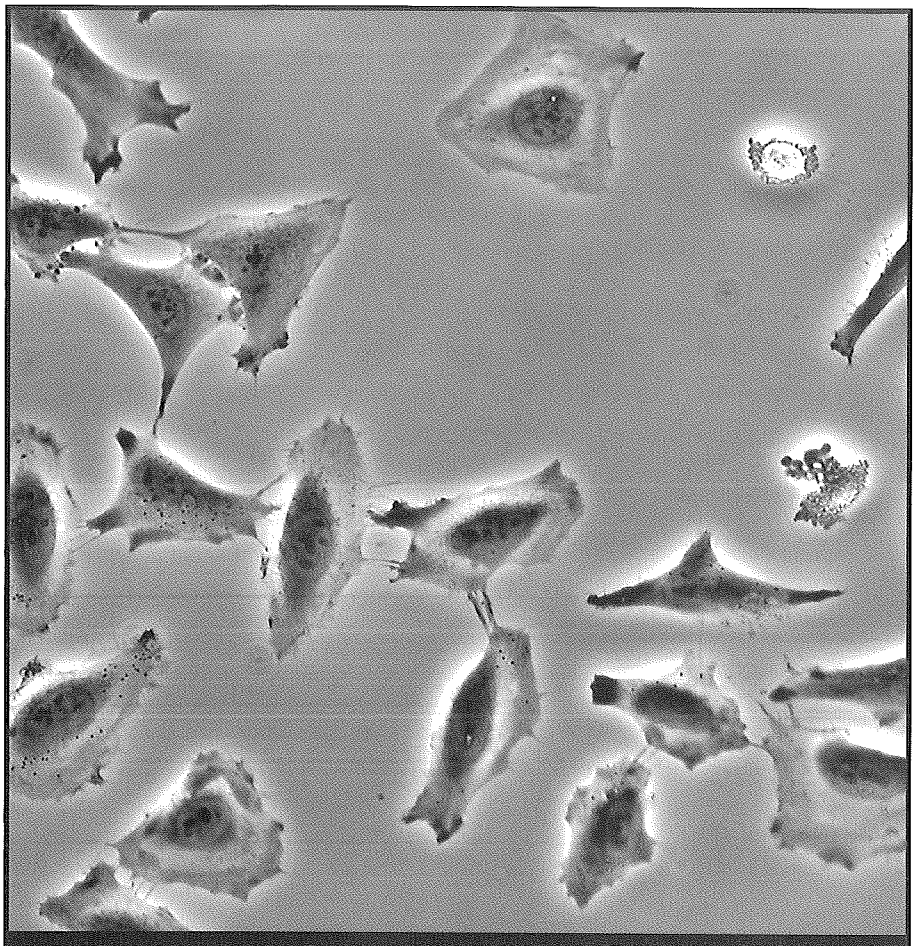
Therefore, lifestyle modification, for example, stopping smoking and reducing the number of sexual partners, can help reduce the risk of cervical cancer.



Many sexually active women have already been infected with the human papillomavirus and would not be adequately protected by the current prophylactic vaccines.

HPV Vaccine

The most prevalent HPV types associated with cervical cancer are HPV-16 and HPV-18, which account for more than 70% of cervical cancer. Two HPV vaccines have shown promise in protecting against HPV-16 and HPV-18 persistent infection and their associated cervical cancer precursor, and cervical cancer. The bivalent vaccine protects against infection with the two most common cancer-causing types of HPV, types 16 and 18, while the quadrivalent vaccine prevents infection with high-risk HPV types 16 and 18 and protects against two low-risk HPV types 6 and 11, which cause about 90% of genital warts. Both vaccines are given in a series of three 0.5 mL injections over 6 months. The vaccine has now been approved in more than 100 countries and has become part of the national immunization programme in countries like the United Kingdom and Australia. It was initially approved for use in females aged 9–26 years, but in some countries, the age range has now been extended to 45.



A long precancerous stage allows for an effective cervical cancer screening programme to diagnose most precancerous lesions, which can be treated before progression to cancer.

Randomized, double-blind, placebo-controlled studies have found that both vaccines are at least 95% effective in preventing HPV-16 or -18 persistent infection and 100% effective in preventing type-specific cervical lesions when given to girls prior to sexual activity or to women without prior infection with these HPV types.[14–16] Vaccination produced antibody titres higher than those after natural infection,[17,18] and vaccine-induced anti-HPV-16 and -18 geometric mean titre (GMT) at 51–53 months were about 17-fold and 14-fold higher than HPV-16 and HPV-18 natural infection, respectively.[15] Vaccine protection appears to be long-lasting. So far, the vaccines are found to be effective for at least 6.5 years.

The most common known adverse events following HPV immunization are discomfort at the injection site, pain, swelling, redness, headache and low-grade fever.[14,16] No serious adverse events have been reported in any of the clinical trials. Although the new HPV vaccines are expected to result in impressive reductions in the risk and incidence of cervical cancer, they cannot replace cervical screening at the moment. Many women have already been infected with HPV if they have been sexually active sometime in their lives, and they would not be adequately protected by the current prophylactic vaccines. Furthermore, only two of the cancer-causing types of HPV, accounting for only 70% of all cervical cancers, are included in the currently available vaccines. Therefore, despite the availability of the vaccines, cervical cancer screening programmes continue to have a definite role in prevention.

SECONDARY PREVENTION: SCREENING, DIAGNOSIS AND TREATMENT

The natural history of cervical cancer is well understood. Studies have demonstrated that invasive cervical cancer arises as a consequence of progression from mild dysplasia through severe dysplasia to carcinoma *in situ*. Some of the preinvasive lesions (cervical intraepithelial neoplasia [CIN]) will regress to normal, but a significant proportion will progress to cervical cancer in 10–15 years' time. With a long precancerous stage, an effective screening programme can potentially diagnose most of the precancerous lesions, which can be treated before progression to cancer. In the last decades, this strategy has greatly contributed to the decreased cervical cancer morbidity in developed countries.

Cytology Screening

For decades, the Papanicolaou (Pap) smear has been used throughout the world to identify precancerous cervical lesions for treatment and follow-up. In developed countries, routine Pap smear screening has contributed to a 70–80% reduction of cervical cancer.[19] However, a single cervical cytology result is relatively insensitive for the detection of cervical precancer and cancer. The sensitivity to detect CIN2/3 lesions ranges from 47% to 62%, and the specificity, from 60% to 95%.[20]

Pap smear failure can be a consequence of sampling technique or the monotony of subjectively processing many samples. Efforts to improve Pap smears in the last decade include the development of liquid-based cytology (LBC), which uses a small amount of fluid to preserve cells collected from the cervix, and automation of the process of preparing smears.

Liquid-based cytology has greater laboratory efficiency and reduces a number of problems, such as poor fixation, uneven thickness of the cell spread, debris and air-drying artifacts.[21] This method improves sample adequacy and sensitivity, but reduces specificity compared with conventional Pap smear. A population-based study of more than 8,000 women in Costa Rica showed that significantly more women were referred to colposcopy where the threshold for referral was atypical squamous cells of undetermined significance (ASC-US) (12.7% versus 6.7% in LBC group and conventional smear group, respectively). However, LBC was more sensitive at detecting high-grade squamous intraepithelial lesions (HSIL) and cancer. LBC detected 92.9% of HSIL and 100% of carcinoma, whereas conventional smears detected 77.8% of HSIL and 90.9% of carcinomas.[22]

The second technological development of significance in cytology is automation, in which computer technology using algorithms of recognition can identify the most abnormal areas of an entire slide and present them for the purpose of reading.[21]

Automation and LBC have the potential to improve the efficiency of cervical cytology testing; however, they increase the cost of screening, which means they may not be well suited for use in low-resource settings.[23]

HPV Testing

It has been well established that cervical neoplasia is caused by persistent infection with certain oncogenic types of HPV. This knowledge has led to the evaluation of HPV testing as a screening tool. The Hybrid Capture (HC) assay is currently the most widely used and the only US Food and Drug Administration HPV test approved for clinical use. The HC2 test can detect 13 types of high-risk HPV. Other HPV DNA testing formats based on polymerase chain reaction (PCR) permit identifying infection with individual oncogenic types. One advantage of HPV DNA testing is that it is not as subjective as cytology screening. Its other advantage is that in addition to identifying those who are at increased risk for developing cervical disease, HPV DNA testing can identify women who already have the disease.[24]

HPV infections are very common in young, sexually active populations. Fortunately, most HPV infections in young women are transient, and only a small proportion of women would become persistently infected with high-risk HPV types.[25] However, in women aged 30 years or older, the HPV DNA positivity rate-drop and transient HPV infection are much less common. HPV DNA testing is particularly valuable in detecting high-grade precancerous lesions in women over age 30, with average sensitivity and specificity at 89% and 90%, respectively.[26] A randomized controlled trial was designed to compare HPV testing (HC2) and the Pap smear in parallel as stand-alone primary screening tests to identify CIN2+ in 10,154 women aged 30–69 years presenting for routine

Liquid-based cytology shows greater laboratory efficiency and reduces a number of problems.

screening. The outcome showed that compared with Pap smear, HPV testing has greater sensitivity for the detection of CIN.[27] In addition, testing for high-risk types of HPV DNA has a very high negative predictive value (NPV), that is, the likelihood of having no disease if the HPV DNA test is negative.[28]

A meta-analysis assessed the accuracy of HPV testing as an alternative to repeat cytology in women who had equivocal results on a previous Pap smear and found that HPV testing has better accuracy (higher sensitivity, similar specificity) than the repeat Pap smear.[29] Another meta-analysis showed that after treatment of cervical lesions, HPV testing more easily detects (with higher sensitivity without lowering the specificity) residual or recurrent CIN than follow-up cytology. Furthermore, compared with cytology with cut-offs at ASC-US or low-grade squamous intraepithelial lesion, primary screening with HC2 generally detects 23% more CIN2/3 or cancer, but is 6% less specific. In comparison with isolated HC2 screening, using combined HPV and cytology screening can identify another 4% more CIN3 lesions, but after incurring a 7% loss in specificity.[30]

Recently, a population-based randomized trial indicated that using HPV DNA testing as the primary screening followed by cytological triage and repeat HPV DNA testing of women with normal cytology who are HPV DNA positive after at least 1 year is a feasible strategy for incorporating HPV testing in primary cervical cancer screening because it improves sensitivity and maintains a high positive predictive value, thus minimizing unnecessary referrals.[31] A few large randomized controlled

trials of HPV testing in primary cervical cancer screening are currently ongoing in the Netherlands, the United Kingdom, Sweden, Finland, Italy, Canada and India. However, HPV DNA testing is expensive and presents some of the same challenges as cytology screening in low-resource areas. For example, the test requires laboratory facilities, special equipment and trained personnel; takes 6 to 8 hours for results; and requires follow-up visits for results and treatment. Fortunately, easier-to-use and less expensive HPV DNA tests are being developed and may revolutionize cervical cancer screening around the globe.

Visual Inspection with Acetic Acid

In developing countries, widespread screenings by Pap smear and HPV DNA test are still too expensive to achieve. Screen-treatment by visual inspection with acetic acid (VIA) and cryotherapy may be the optimal screening strategy in these countries. VIA involves applying 3% to 5% acetic acid (vinegar) to the cervix using a spray or a cotton swab and observing the cervix with the naked eye after 1 minute. If characteristic, well-defined aceto-white areas are seen adjacent to the transformation zone, the test is considered positive for precancerous cell changes or early invasive cancer.[32] VIA does not require laboratory staff training. The results are immediately available, allowing treatment during a single visit and thus reducing loss to patient follow-up. The sensitivity of VIA is equivalent to or better than that of a Pap smear, although its specificity is lower.[33,34]

In a cluster-randomized trial in the Dindigul district in India, of the 49,311 eligible women aged 30–59 years in the VIA group, 31,343 (63.6%) were screened during 2000–2003; 30,958 women in the control group received routine care. A significant 25% reduction in cervical cancer incidence and 35% reduction in mortality were reported 7 years after the beginning of screening in this study.[35]

Like the Pap smear, visual inspection is subjective, and supervision is needed for quality control of visual inspection methods. VIA might not work as well in postmenopausal women because the transformation zone recedes into the cervical canal at menopause.[34] A study has shown that VIA also can be used in follow-up post cryotherapy with a negative predictive value of 99.7% and an accuracy of 93.7%, which is comparable to those of Pap smear.[36]

In low-resource countries, transportation, time and other access issues make follow-up visits difficult. Through screen-and-treat programmes, the women are less likely to be lost to follow-up before being treated. Screen-and-treat programmes have been evaluated in Thailand, Bangladesh, India, South Africa and Ghana with good results. The data show that VIA and cryotherapy, in one or two clinical visits, without an intermediary colposcopic diagnostic step, is one of the most cost-effective alternatives to conventional multivisit strategies.[37–40]

Visual Inspection with Lugol's Iodine

Visual inspection with Lugol's iodine (VILI) is similar to VIA, but uses Lugol's iodine to map the cervix, followed by an examination for mustard-yellow areas. The screening and treatment also can be done in a single visit. A multicentre study in India and Africa showed the sensitivity and specificity of VILI to detect high-grade CIN were 92% and 85%, respectively.[41] In contrast, in a Latin American study, VILI was found to have a sensitivity of 53% and a specificity of 78% in detecting high-grade CIN. Therefore, further studies of the accuracy of VILI are warranted.[42]

CONCLUSION

The arrival of HPV vaccination has brought cervical prevention into a new era. This effective primary preventive measure also has major implications for secondary preventive measures. Although the current HPV vaccines appear to be very promising, there are still some unresolved issues, such as the duration of prevention, the limited coverage of HPV genotypes, the accessibility in developing countries because of high cost and the need to vaccinate men. The role of HPV testing as a screening method for precancerous lesions will need to be continually evaluated, particularly among the vaccinated population. Meanwhile, achieving good preventive measures in low-resource settings remains an important issue, because these areas have the highest cervical cancer incidence.

About the Authors

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