

WJCO 5th Anniversary Special Issues (3): Cervical cancer**Cervical cancer: Can it be prevented?**

Pakhee Aggarwal

Pakhee Aggarwal, Consultant Obstetrics and Gynaecology, Fortis Healthcare (East) Management Ltd, Aashlok Hospital, Safdarjung Enclave, New Delhi 110029, India

Author contributions: Aggarwal P was responsible for writing and editing this paper and critically revising it for intellectual content.

Correspondence to: Pakhee Aggarwal, MS (Obstetrics and Gynaecology), MICO, MRCOG, MIPHA, Consultant Obstetrics and Gynaecology, Fortis Healthcare (East) Management Ltd, Aashlok Hospital, Safdarjung Enclave, 4187, B-5 and 6, Vasant Kunj, New Delhi 110070, India. pakh_ag@yahoo.com
Telephone: +91-98-68602466

Received: December 28, 2013 Revised: May 26, 2014

Accepted: June 27, 2014

Published online: October 10, 2014

Abstract

Cervical cancer prevention requires a multipronged approach involving primary, secondary and tertiary prevention. The key element under primary prevention is human papilloma virus (HPV) vaccination. So far, only prophylactic HPV vaccines which prevent HPV infection by one or more subtypes are commercially available. Therapeutic HPV vaccines which aid in clearing established infection are still under trial. Secondary prevention entails early detection of precancerous lesions and its success is determined by the population coverage and the efficacy of the screening technique. A number of techniques are in use, including cytology, visual inspection (using the naked eye, magnivisualizer, acetic acid and Lugol's iodine), HPV testing and a combination of these methods. Updated screening guidelines have been advocated by the American Cancer Society in light of the role of HPV on cervical carcinogenesis. Recent research has also focussed on novel biomarkers that can predict progression to cancer in screen positive women and help to differentiate those who need treatment from those who can be left for follow-up. Last but not the least, effective treatment of precancerous lesions can help to reduce the incidence of invasive cervical cancer and this constitutes tertiary prevention.

A combination of these approaches can help to prevent the burden of cervical cancer and its antecedent morbidity and mortality, but all of these are not feasible in all settings due to resource and allocation constraints. Thus, all countries, especially low and middle income ones, have to determine their own cocktail of approaches that work before we can say with certainty that yes, cervical cancer can be prevented.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

Key words: Cervical cancer; Prevention; Screening; Human papilloma virus; Pap smear

Core tip: While cervical cancer is not new, approaches to prevent the burden of this deadly disease are constantly being re-invented, be it human papilloma virus (HPV) testing or screening strategies. Novel biomarkers than can predict which HPV positive lesions will progress into cancer are the need of the hour. Along with early diagnosis of pre-invasive lesions, the other preventive aspect includes prophylactic vaccines which have flooded the scene, but their true impact remains to be gauged as the precancerous phase of cervical cancer is longer than the vaccine has been around. Only time can answer the question: can we truly prevent cervical cancer?

Aggarwal P. Cervical cancer: Can it be prevented? *World J Clin Oncol* 2014; 5(4): 775-780 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v5/i4/775.htm> DOI: <http://dx.doi.org/10.5306/wjco.v5.i4.775>

INTRODUCTION

Cervical cancer is the most common cause of deaths due to any cancer in developing countries and the number of these is ten times that in developed countries. It is the third most common cancer in women after breast and

Table 1 Risk factors for cervical cancer

Causal agent	Relative risk
Low socio-economic class	1.5
Low educational level	2-3
Early age at first coitus	2-4
Multiple sexual partners	2-5
Early age at first pregnancy	2-4
Multiparity	2-4
Long term use of oral contraceptives	1.5-2
History of sexually transmitted infections	4-10
History of genital warts	18
Cigarette smoking	2-4
Diet low in folates, carotene and vitamin C	2-3
Lack of routine cytological screening or prior abnormal smears	2-6
HIV	2.5
Immunosuppression	5.7

HIV: Human immunodeficiency virus.

colorectal cancer, with more than 530000 cases in 2008, 85% of these in developing countries. The mortality: incidence ratio is 52% and there were 275000 deaths in 2008, 88% of them in developing countries^[1,2].

The case for prevention of cervical cancer is thus a strong one that would serve to prevent mortality in many women and morbidity in many others. We know that cervical cancer is preventable, but the bigger question is, can it be prevented?

Prevention of any condition is described in terms of primary, secondary and tertiary prevention. While primary prevention deals with modification of risk factors to prevent disease occurrence, secondary prevention essentially signifies early diagnosis and treatment, while tertiary prevention seeks to limit the disability caused by the condition^[3]. Cervical cancer is particularly amenable to prevention as it has a long pre-clinical phase and the natural history of cervical carcinogenesis is well researched. In addition, treatment of pre-invasive lesions has been shown to reduce the incidence of invasive cervical cancer.

PRIMARY PREVENTION

In terms of cervical cancer, primary prevention involves education about safe sexual practices and *human papilloma virus* (HPV) vaccination^[4]. This is because HPV is known to be a necessary cause of cervical cancer and it is the persistence of this infection over decades which can lead to precancerous changes in the cervix and eventually cancer. The first vaccine licensed was Gardasil (Merck, Pennsylvania) in 2006 which protects against HPV 6, 11, 16 and 18, while Cervarix (Glaxo Smith Klein, Belgium) which was licensed in 2009 protects against HPV 16 and 18. Both of these are prophylactic vaccines which have now been introduced in over 80 countries. Short term data indicates that they are safe, immunogenic and efficacious in preventing HPV infection and hence precancerous lesions by the respective HPV types. There is

also some evidence of cross-protection against closely related HPV types. They are less effective in established infection. The best evidence of HPV vaccination success comes from Australia, where introduction of nationwide HPV vaccination resulted in a decrease in the incidence of high grade cervical abnormalities within 3 years after vaccination^[5]. Recent data indicates that two doses of vaccine may be as protective as three doses^[6] and this has implications for use where the utilization is limited by costs.

There is another kind of vaccine, the therapeutic vaccines which help in the clearance of HPV infections by generating T-cell mediated immunity against the HPV E6 and E7 antigens. These have been shown to be efficacious under trial conditions^[7].

However, although HPV infection is the most common, it is not the only causal agent of cervical cancer. As understood by the model for cervical carcinogenesis, there are various other behavioral and demographic risk factors that increase the relative risk of developing cervical cancer. These are given in Table 1.

Others factors like older age, racial factors and genetic predisposition are non-modifiable risk factors^[8]. There is some data to indicate that consumption of high amounts of whole fruits and vegetables, fish and nuts which provide a rich source of antioxidants like vitamin C, E, carotene, lutein and lycopene, and vitamin A, calcium and poly-unsaturated fatty acids can significantly reduce the risk of CIN^[9]. The mechanism of action is purported to be by enhancing HPV clearance while still in the transient phase, inhibiting the expression of E6 and E7, preventing DNA damage and reducing immunosuppression^[9].

SECONDARY PREVENTION

Secondary prevention involves screening asymptomatic patients or carrying out definitive tests in symptomatic or screen positive patients to pick up precancerous lesions before they turn into cancer. A number of methods are available for cervical cancer screening. Observational studies have shown that introduction of any regular cervical cancer screening program results in a fall in the incidence of invasive cervical cancer and cancer deaths. The Nordic countries are a prime example where introduction of organized cervical screening reduced the incidence of cancer deaths between 10%-80%.

Various modalities employed for screening preinvasive disease are: (1) cervical cytology - both conventional and liquid-based; (2) direct visual inspection (DVI); (3) visual inspection using 3%-5% acetic acid (VIA); (4) visual inspection using 3%-5% acetic acid and magnification (VIAM); (5) visual inspection using Lugol's iodine (VILI); (6) HPV DNA testing; (7) speculscopy; and (8) polar probes. Other modalities like colposcopy, cervicography and microcolpohysteroscopy can be used for further evaluation of abnormal results.

Cervical cytology is the globally preferred screening method and has been shown to reduce the incidence

Table 2 American College of Obstetricians and Gynecologists guidelines for cervical cancer screening

Commence	Frequency of smears (Pap or LBC) and HPV testing	Discontinue	HPV DNA
21 yr	1 3 yearly smears for < 30 yr 2 3 yearly smears or 5 yearly co-testing for > 30 yr (if 2 previous smears normal) 3 3 yearly smears or 5 yearly co-testing for those previously treated for CIN2/3 or cancer (up to 20 yr)	1 > 65 yr 2 After hysterectomy for benign disease with no history of CIN	For women > 30 yr, two options to manage Positive test: Repeat co-testing at 12 mo; Test for HPV 16/18 and colposcopy if positive

HPV vaccination does not change these guidelines. HPV: Human papilloma virus; LBC: Liquid based cytology.

of invasive cervical cancer by up to 80%^[10], while other methods of screening have generally been used in project settings. However, the fall in incidence with Pap smear based screening is directly linked to the frequency of screening and the proportion of population covered by screening. The conventional Papanicolaou test is done to examine exfoliated cells from the ectocervix and the endocervix using a wooden Ayre spatula and cytobrush. The smear is prepared and fixed with 95% ethylene glycol. Slides are stained using the Papanicolaou method and graded according to the revised Bethesda system. Although cytology has a high specificity of 95%-99%, pooled data has shown the sensitivity of a single Pap smear to be as low as 51%^[11]. For liquid based cytology (LBC), the method involves using a cytobrush which is rotated by 360 degrees five times around the cervix and the exfoliated cells are stirred in a proprietary solution. This reduces specimen inadequacy (which can cause false negative smear results) by 80% but adds to the cost. In addition, a single specimen may be used for HPV, chlamydia and gonorrhea testing. Screening guidelines have been advocated by various societies.

The latest screening guidelines^[12] by the American College of Obstetricians and Gynecologists (ACOG) published in 2012 are given in Table 2.

Where resources are limited, the World Health Organization recommends that the highest priority group for screening is those aged 35 or over and that screening every 5 years for a total of 3 tests in a lifetime will achieve a major impact. In low resource settings, screening using HPV as a primary test followed by further triaging for treatment using cytology or VIA of HPV positive women can cut costs while maximising benefits of screening.

Direct (unaided) visual inspection (DVI) is advocated in low resource settings where no other method is available as the incidence of CIN in a clinically unhealthy cervix may be as high as 9% compared to 0.9% in a healthy cervix^[13]. DVI can detect cancer early and improve survival rates and thus should be done in all patients, even if pregnant.

Aided visual inspection methods which include VIA, VIAM and VILI are simple, low tech approaches that are minimally reliant on infrastructure, assuming that basic facilities for performing a speculum examination are available. Non-physicians can perform the procedure if they receive adequate and ongoing training. Furthermore, results of the procedure are available immediately, mak-

ing it possible, in principle, to provide treatment during the same visit (screen-and-treat or single-visit approach). VIA involves swabbing the cervix with 5% acetic acid and inspecting the cervix in good light after 1 min to look for acetowhite lesions. For VIAM, the cervix is inspected as before but by using a self-illuminated hand held device. The disadvantages are low specificity compared to cytology, potential for over-diagnosis and over-treatment, observer dependency and usefulness in detecting ectocervical disease only. Our own institutional data (including over 1200 patients) found the sensitivity and specificity of VIA to be between 91%-96% and 31%-82% respectively^[13,14]. The large variation in specificity indicates that several variables affect the test characteristics of VIA, including light source, observer training, criteria for test positivity and the presence of co-existing infection, inflammation and metaplasia. VIAM offers the advantage of 4 × magnification using a hand held battery powered device and improved the specificity over VIA from our data^[14]. It can supplement VIA in doubtful cases where colposcopy is not available as a secondary triage. In low resource settings, primary screening by VIA/VIAM is more cost effective compared to universal Pap smear and can be used to take a guided biopsy and endocervical curettage.

HPV DNA testing

Two types of tests for HPV DNA are currently in use; one is a nucleic acid hybridization assay with signal amplification for the qualitative detection of high risk HPV types in cervical specimens (Digene Hybrid Capture 2 High Risk HPV DNA TestTM; Cervista HPV HR TestTM); the other is a polymerase chain reaction based assay (HPV DNA Nested Polymerase Chain Reaction Detection KitTM). Detection of high risk HPV DNA increases the sensitivity of detection for both squamous and glandular abnormalities; however, it does not have the analytical specificity that can help to decide which lesions need treatment and those that will regress on follow-up.

A new test for HPV E6/E7 mRNA (PreTect HPV-ProoferTM assay and APTIMATM assay) is under research and is based on the fact that mRNA levels are directly correlated to the severity of the lesion and can predict progression to cancer with higher specificity than HPV DNA testing alone. This can be used to stratify high risk HPV positive women that need treatment. The reported sensitivity and specificity range from 0.41-0.86

and 0.63-0.97 respectively for PreTect based on pooled data^[15]. FDA approval is awaited.

In both triage (investigation of minor abnormalities detected by cytology) and screening studies (when both cytology and HPV testing are jointly performed) the cross-sectional sensitivity of HPV test is high and so is the negative predictive value (> 97%). The combination of the high sensitivity of HPV DNA testing and the high specificity of cytology can increase the screening interval for testing in women negative by both methods. Such a combined test was approved by the FDA in 2003 for primary screening of low risk women aged ≥ 30 years^[16]. In low and middle income countries, integrating the highly accurate HPV testing with the triaging capacity of VIA in “screen and treat” protocols can offer the dual benefits of maximizing detection using HPV and then using VIA to triage them for treatment^[17]. Despite the high cost of HPV testing compared to VIA alone, this can turn out to be cost effective in the longer run due to the costs saved on diagnosis and treatment of cancer. The advantages of HPV DNA testing are the objectivity of the test, possibility of complete automation, built in quality control, opportunities for self sampling and high sensitivity. Its disadvantages are cost, dependence on a single manufacturer (so far only HC2 is FDA approved and validated), requirement of a molecular diagnostic lab, low specificity in younger women and populations with significant HIV seropositivity, and follow up visits for test results and treatment.

Speculoscopy refers to direct observation of the cervix under 4-6 \times magnification using a blue-white chemiluminescent light source to enhance visualization of abnormal tissue after acetic acid application. This is a variant of the VIA designed to increase its specificity but it is marginally more expensive.

Polar probe is a pen-sized device (which is moved across the cervix) of electro-optical systems to identify cancer or pre-cancerous cells in cervical tissue by measuring the response of cervical tissue to light together with tissue capacitance of epithelial, basal and stromal layers. In a multicentric study, it was found to be as sensitive as a top quality Pap smear. It also has a high accuracy with instant report which prevents loss to follow up. Due to the objective, self-checking digital system, there is no subjective error of interpretation or the need for trained personnel to read the smear.

Colposcopy provides a magnified (up to 40 \times) stereoscopic view of the cervix and vagina and is a sensitive method for diagnosing CIN and invasive cancers. It helps in localizing abnormal areas from where a biopsy can be taken and accurate grading and conservative management of CIN is possible. It can supplement cytology and also triage cases that are a doubtful positive on VIA/VIAM. Its disadvantages are bulky and costly equipment and the need for experienced personnel.

Cervicography is a technique that attempts to reproduce colposcopy photographically. A photograph of the cervix (cervigram slide) is taken with a specially designed

camera (cerviscope) after the application of acetic acid and sent to an expert for interpretation. Cervicography has a better sensitivity than cytology (89% *vs* 52%), with similar specificity (94% *vs* 92%)^[18]. Cervicography is a highly sensitive tool for evaluating the ectocervical transformation zone but is unable to evaluate the endocervical canal. The expense of the instrument and the costs of photographs make it unlikely to be used for population screening, although it can be used in combination with a Pap smear to facilitate the selection of therapy for patients with an abnormal Pap test.

Microcolpohysteroscopy permits a naked eye view of the endocervix to evaluate the cervical canal *in situ*, thus obviating the need for a cone biopsy. It focuses on cells that have not been desquamated within their topographic and architectural context. A magnification of 20 \times gives visualization comparable to colposcopy, while 150 \times gives visualization comparable to cytology.

Recent research has centered on identifying the host genes up regulated in association with HPV infection, determining their suitability as “surrogate markers” for HPV infection, and using them to identify HPV-associated epithelial lesions in tissue or cytological specimens^[19]. These can help to increase diagnostic accuracy of cervical tissue specimens and provide information on risk of progression. These are given in Table 3.

Other newer technologies like optical imaging, spectroscopy and high-resolution imaging methods provide *in vivo* diagnosis with high sensitivity and specificity and are anticipated to improve conventional cervical cancer screening. They are based on the concept of morphological and biochemical alteration in the properties of cervical tissue in response to malignant transformation. In addition, contrast agents that target against specific neoplastic biomarkers can enhance the effectiveness of this new technology^[20].

The cycle of testing (using a sensitive test at regular intervals), diagnosis (using a highly specific test), treatment (with effective methods and by trained staff) and follow-up (as a part of an organized program with high population coverage) should be completed to ensure the success of screening.

TERTIARY PREVENTION

Tertiary prevention seeks to limit disability and promote rehabilitation. As cervical cancer has a long history in the form of precancerous lesions, diagnosis in the early phase and proper management (by cryotherapy or large loop excision of the transformation zone (LLETZ)) will prevent the progression to invasive cancer. Both can be done in the outpatient setting. While cryotherapy is useful for lesions involving maximum 1-2 contiguous quadrants of the cervix and no endocervical involvement, LLETZ can treat the entire transformation zone as well as a lesion extending not more than 1 cm into the endocervical canal. It also has the advantage of removing the specimen for histological analysis^[21]. Complication rate is less

Table 3 Biomarkers in cervical dysplasia

Biomarker	Significance
L1 capsid protein	Represents approximately 90% of the total protein on the virus surface and is generally detectable during the reproductive phase of HPV infection. The L1 protein is abundant in productive infections (CIN 1), found only in rare cases of CIN2/3, and not produced in carcinomas
p16INK4a (CINtec™)	Surrogate marker of HPV E7-mediated pRb catabolism, providing evidence of transformation of the cervical mucosa. On immunohistochemistry, diffuse staining for p16INK4a is present in almost all cases of CIN2, CIN3, squamous cell carcinoma and endocervical glandular neoplasia; however, it is rarely detected in benign squamous mucosa or CIN 1 lesions caused by low risk HPV types
Ki-67	Proliferation marker confined to the parabasal cell layer of normal stratified squamous mucosa but shows expression in the stratified squamous epithelium in CIN lesions in correlation with the extent of disordered maturation, but cannot discriminate HPV-mediated dysplasia from proliferating cells in benign reactive processes
DNA Aneuploidy	HPV infection leads to DNA hypermethylation, disruption of the normal cell cycle, and chromosomal aberrations, all of which may lead to changes in DNA content. Aneuploidy increases progressively from CIN1 to CIN3
MCMs (ProExC test™)	MCMs are required for the origination of DNA replication and are overexpressed in cervical high-grade dysplasia and carcinoma, but can also be seen in some benign cycling squamous and glandular cells
FISH technology	One of the most consistent chromosomal abnormalities in cervical carcinoma is gain of chromosome arm 3q (in about 70%), which can be detected by FISH. TERC gene in this region is amplified in progression to CIN3

FISH: Fluorescent *in situ* hybridization; MCAs: Minichromosome maintenance proteins; TERC: Telomerase RNA component.

Table 4 Management of preinvasive cancer (American Society for Colposcopy and Cervical Pathology 2012 guidelines)

Lesion on biopsy	Other features	Management
CIN 1	Preceding cytology of ASC-US, ASC-H, LSIL	Follow up with cytology (6, 12 mo) and HPV testing (12 mo)
CIN 1	Preceding cytology of HSIL, AGC-NOS	Either of these: Diagnostic excisional procedure or review of findings or observation with HPV and cytology (12 and 24 mo) (only if colposcopy satisfactory and ECC negative)
CIN 1	Adolescent (< 20 yr)	Follow up with cytology (12 mo)
CIN 1	21-24 yr	Follow up with cytology and colposcopy (6 monthly, up to 2 yr)
CIN 2/3	Satisfactory colposcopy	Either excision or ablation of transformation zone
CIN 2/3	Unsatisfactory colposcopy or recurrence or endocervical disease	Diagnostic excisional procedure
CIN 2/3	Adolescent (< 20 yr) and young women (21-24 yr)	Observation with cytology and colposcopy (only if colposcopy satisfactory) or treatment using excision or ablation of transformation zone
Adenocarcinoma <i>in situ</i>	Specimen from diagnostic excisional procedure	Hysterectomy preferred (rarely conservative management if margins negative and future fertility desired)

HPV: *Human papilloma virus*. CIN: Cervical intraepithelial neoplasia, ASC-US: Atypical squamous cells - undetermined significance; ASC-H: Atypical squamous cells - cannot exclude; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; ECC: Endocervical curettage.

with cryotherapy and includes watery discharge for 3-4 wk, cervical stenosis (< 1%) and vaginal bleeding (very rare). It has no adverse effects on fertility and pregnancy and can be carried out by the average gynecologist. LLETZ on the other hand, requires more technical skill, a ready supply of electricity and is associated with severe perioperative bleeding (< 2%), cramping abdominal pain and effects on future fertility (infertility, preterm labor, cervical stenosis and dystocia).

The American Society of Colposcopy and Cervical Pathology has issued guidance for management of preinvasive cervical lesions diagnosed on biopsy^[22]. These are given in Table 4. Similar guidelines are also in place for a diagnosis based on Pap smear.

Pregnancy constitutes a special situation where the only indication for treatment is suspected invasive cancer. Both CIN 1 and CIN 2/3 require follow up during pregnancy (no more frequently than 12 wk) as the risk of progression to invasive cervical cancer is minimal and the rate of spontaneous regression postpartum is relatively high. Re-evalua-

tion is recommended no sooner than 6 wk postpartum.

Thus, prevention of cervical cancer involves a multi-pronged approach of education, creating awareness, advocacy, public-private partnerships for HPV vaccination, screening and early treatment of precancerous lesions before they develop into cancer. The extent of focus on each of these measures may vary between communities and countries based on the availability of resources and healthcare commitments. A holistic approach to prevention involving locally effective measures and treatment protocols and evaluating their adherence and success over time can help to tailor programs and policies to maximize the benefits for cervical cancer prevention.

Cervical cancer is preventable. Cervical cancer can be prevented. The extent to which we achieve this goal depends on us.

REFERENCES

- 1 International Agency for Research on Cancer, GLOBOCAN

- database, 2008. Cited 2013-12-10. Available from: URL: <http://globocan.iarc.fr/factsheet.asp>
- 2 **Aggarwal P**, Batra S, Gandhi G, Zutshi V. Can visual inspection with acetic acid under magnification substitute colposcopy in detecting cervical intra-epithelial neoplasia in low-resource settings? *Arch Gynecol Obstet* 2011; **284**: 397-403 [DOI: 10.1007/s00404-010-1673-0. Epub 2010 Sep 24]
 - 3 **Park K**. Park's Textbook of Preventive & Social Medicine. 18th ed. Jabalpur: Banarsidas Bhanot, 2005: 37
 - 4 Centres for Disease Control and Prevention. Frequently Asked Questions About HPV Vaccine Safety [online]. Cited 2012-04-08. Available from: URL: http://www.cdc.gov/vaccinesafety/Vaccines/HPV/hpv_faqs.html
 - 5 **Brotherton JM**, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet* 2011; **377**: 2085-2092 [PMID: 21684381 DOI: 10.1016/S0140-6736(11)60551-5]
 - 6 **Kitchener HC**, Denton K, Soldan K, Crosbie EJ. Developing role of HPV in cervical cancer prevention. *BMJ* 2013; **347**: f4781 [PMID: 23926316 DOI: 10.1136/bmj.f4781]
 - 7 **Solomon D**, Castle P, Hildesheim A, Katki HA, Schiffman M, Wacholder S. HPV vaccination in women aged 24-45 years. *Lancet* 2009; **374**: 1239; author reply 1239-1240 [PMID: 19819386 DOI: 10.1016/S0140-6736(09)61782-7]
 - 8 **Posadas EM**, Kotz HL. Cervical Cancer. In: Bethesda Handbook of Clinical Oncology, Ed. Abraham J, Gulley JL, Allegra CJ (Eds.) Philadelphia PA: Lippincott Williams & Wilkins, 2005: 245-246
 - 9 **Chih HJ**, Lee AH, Colville L, Binns CW, Xu D. A review of dietary prevention of human papillomavirus-related infection of the cervix and cervical intraepithelial neoplasia. *Nutr Cancer* 2013; **65**: 317-328 [PMID: 23530631 DOI: 10.1080/01635581.2013.757630]
 - 10 **Miller AB**, Nazeer S, Fonn S, Brandup-Lukanow A, Rehman R, Cronje H, Sankaranarayanan R, Koroltchouk V, Syrjänen K, Singer A, Onsrud M. Report on consensus conference on cervical cancer screening and management. *Int J Cancer* 2000; **86**: 440-447 [PMID: 10760836 DOI: 10.1002/(SICI)1097-0215(20000501)86]
 - 11 **McCrorry DC**, Matchar DB, Bastian L, Datta S, Hasselblad V, Hickey J, Myers E, Nanda K. Evaluation of cervical cytology. *Evid Rep Technol Assess (Summ)* 1999; **(5)**: 1-6 [PMID: 11925972]
 - 12 **Saslow D**, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain JM, Garcia FA, Moriarty AT, Waxman AG, Wilbur DC, Wentzensen N, Downs LS, Spitzer M, Moscicki AB, Franco EL, Stoler MH, Schiffman M, Castle PE, Myers ER, Chelmon D, Herzig A, Kim JJ, Kinney W, Herschel WL, Waldman J. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *J Low Genit Tract Dis* 2012; **16**: 175-204 [PMID: 22418039]
 - 13 **Goel A**, Gandhi G, Batra S, Bhamhani S, Zutshi V, Sachdeva P. Visual inspection of the cervix with acetic acid for cervical intraepithelial lesions. *Int J Gynaecol Obstet* 2005; **88**: 25-30 [PMID: 15617701 DOI: 10.1016/j.ijgo.2004.09.018]
 - 14 **Aggarwal P**, Batra S, Gandhi G, Zutshi V. Comparison of Papanicolaou test with visual detection tests in screening for cervical cancer and developing the optimal strategy for low resource settings. *Int J Gynecol Cancer* 2010; **20**: 862-868 [PMID: 20606535 DOI: 10.1111/IGC.0b013e3181e02f77]
 - 15 **Sahasrabuddhe VV**, Luhn P, Wentzensen N. Human papillomavirus and cervical cancer: biomarkers for improved prevention efforts. *Future Microbiol* 2011; **6**: 1083-1098 [PMID: 21958146 DOI: 10.2217/fmb.11.87]
 - 16 **Wright TC**, Schiffman M, Solomon D, Cox JT, Garcia F, Goldie S, Hatch K, Noller KL, Roach N, Runowicz C, Saslow D. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol* 2004; **103**: 304-309 [PMID: 14754700 DOI: 10.1097/01.AOG.0000109426.82624.f8]
 - 17 **Sahasrabuddhe VV**, Parham GP, Mwanahamuntu MH, Vermund SH. Cervical cancer prevention in low- and middle-income countries: feasible, affordable, essential. *Cancer Prev Res (Phila)* 2012; **5**: 11-17 [PMID: 22158053 DOI: 10.1158/1940-6207.CAPR-11-0540]
 - 18 **Kesic VI**, Soutter WP, Sulovic V, Juznic N, Aleksic M, Ljubic A. A comparison of cytology and cervicography in cervical screening. *Int J Gynecol Cancer* 1993; **3**: 395-398 [PMID: 11578375 DOI: 10.1046/j.1525-1438.1993.03060395.x]
 - 19 **Hwang SJ**, Shroyer KR. Biomarkers of cervical dysplasia and carcinoma. *J Oncol* 2012; **2012**: 507286 [PMID: 22131995 DOI: 10.1155/2012/507286]
 - 20 **Orfanoudaki IM**, Kappou D, Sifakis S. Recent advances in optical imaging for cervical cancer detection. *Arch Gynecol Obstet* 2011; **284**: 1197-208 [PMID: 21800084 DOI: 10.1007/s00404-011-2009-4]
 - 21 **Sellers JW**, Sankaranarayanan R. Colposcopy & the treatment of Cervical Intraepithelial Neoplasia: a beginner's manual. Lyon: IARC Press, 2003: 95-111
 - 22 **American Society for Colposcopy & Cervical Pathology**. Updated consensus guidelines for managing abnormal cervical cancer screening tests and cancer precursors. Cited 2013-12-16. Available from: URL: <http://www.asccp.org/Portals/9/docs/Algorithms 7.30.13.pdf>

P- Reviewer: Ekwueme DU S- Editor: Ji FF
L- Editor: Roemmele A E- Editor: Lu YJ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

