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Journal of SAFOMS

The South Asian Federation of Menopause Societies

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Journal of SAFOMS

1. Aims and Scope

The importance of a middle-aged woman in a South Asian family is known to everyone. The activities performed by her cannot be easily done by any other member of the family anywhere in the world.

It is also a known fact that these are the women who face the most problems regarding their health because of menopause. Keeping this in mind, South Asian Federation of Menopause Societies (SAFOMS) has published this journal for dealing with the chronic health problems faced by the South Asian women during perimenopause and menopause.

The aims and objectives of this journal are as follows:

- To create awareness of the various chronic health diseases and distress caused to a South Asian woman going through menopause.
- To promote a multidisciplinary multifactorial comprehensive approach, medical and non-medical, to the care of these women.
- To help the patients and family physicians understand the need of regular medical check-ups and follow-ups with their gynecologists, especially during and after the transitional period.
- To regularly update doctors and health professionals in the field of menopausal medicine, to ensure appropriate health care for these women.
- To facilitate exchange of ideas and experiences of different disciplines since the physical, mental and emotional health of women in the years after menopause is truly multidimensional and multidisciplinary.
- To collect information and data with particular reference to the South Asian menopausal women.
- To encourage research on relevant aspects in the South Asian context.

2. Ethical Considerations

Investigation and surgery on human subjects should conform to the guidelines noted in the World Health Organization Chronicle 1976;30:360-362.

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Informed Consent

Informed consent of the patients must be taken before they are considered for participation in the study. Patient identifying information, such as names, initials, hospital numbers, or photographs should not be included in the written descriptions. Patient consent should be obtained in written and archived with the authors.

Protection of Human Subjects and Animals in Research

When conducting experiments on human subjects, appropriate approval must have been obtained by relevant ethics committees. All the procedures must be performed in accordance with ethical standards of the responsible ethics committee both (institutional and national) on human experimentation and the Helsinki Declaration of 1964 (as revised in 2008). When reporting experiments on animals, authors must follow the institutional and national guidelines for the care and use of laboratory animals.

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Editorial

HUMAN PAPILLOMAVIRUS AND ITS TESTING

INTRODUCTION

Genital human papillomavirus (HPV) infections are the most common of all sexually transmissible infections and the rate of HPV transmission is even higher when compared with human immunodeficiency virus or herpes simplex virus, type II, with the median transmissibility being 40% per coital act.[1,2] Human papillomavirus is one of the rare viruses and its persistence has carcinogenic potential contributing as the underlying cause of cervical, vulvar, vaginal, anal, and oropharyngeal cancers. Any variable related to sexual activity, including young age, number of sexual partners, any new sexual partner, and having sex with partners who have other partners—both men and women—is a risk factor to acquire genital HPV infection and to easily spread through direct sexual contact from the skin and mucosa of infected partner to noninfected partner while other modes of spread can be via vaginal, anal, or oral sex (Table 1).[3]

STRUCTURE OF HPV

The HPV consists of 8000-base pair-long circular deoxyribonucleic acid (DNA) molecules wrapped in a protein shell containing two molecules, L1 and L2. Its genome is composed of six early genes and two late genes and a noncoding region. Once the virus invades a cell, the early proteins (E1, E2, E3, E4, E5, E6, and E7) are transcribed first, followed by the late proteins (L1 and L2), each of which is necessary for viral replication and formation of newly formed virus particles in infected cells.[4] This tumor virus causes epithelial proliferation at cutaneous and mucosal surfaces.[5]

Presently, there are 148 recognized HPV types classified into 33 species[6] including high-risk HPV (hrHPV) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82, which are considered carcinogenic.[7]

The HPVs infect and survive in squamous epithelial cells and therefore are present on the surface of the skin and mucosal membranes, causing epithelial proliferation at mucocutaneous surfaces (Fig. 1 and Table 2).

Table 1: Types of cancer caused by HPV

Cancer	*Points*
Cervical cancer	HPV types 16 and 18 are responsible for about 70% of all cases
Anal cancer	95% of anal cancers are caused by HPV, mostly type 16
Oropharyngeal cancers	Cancers of the middle part of the throat, including the soft palate, the base of the tongue, and the tonsils, mostly by type 16 in the United States
Rarer cancers	65% of vaginal cancers, 50% of vulvar cancers, 35% of penile cancers mostly by type 16

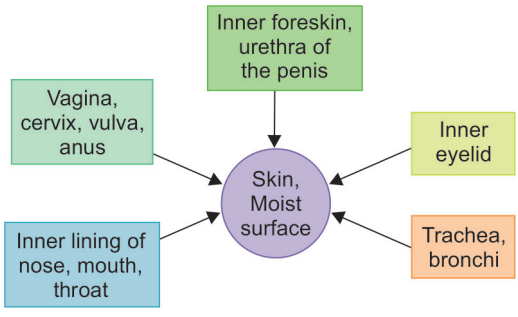
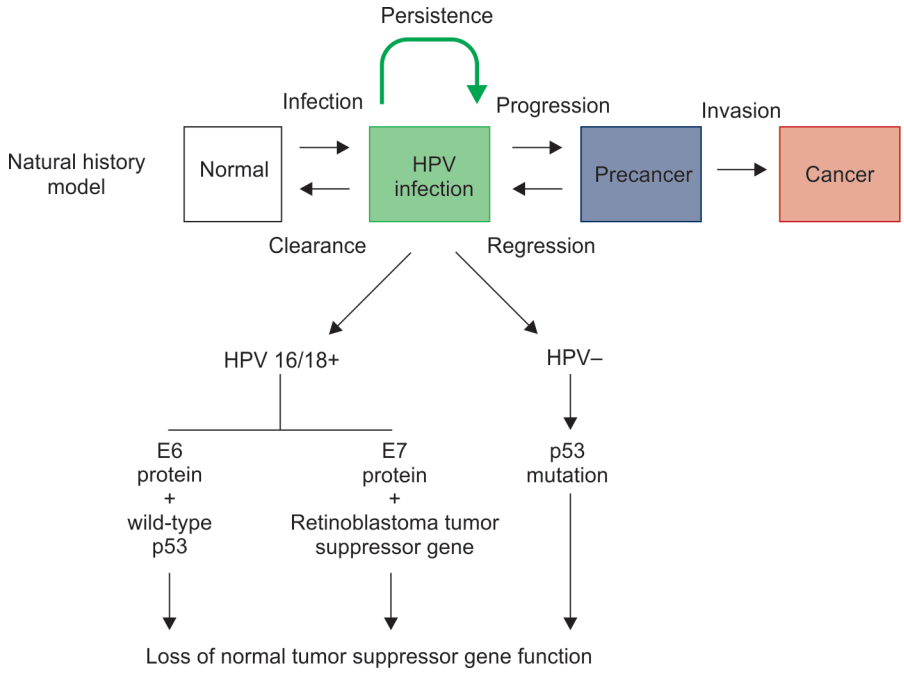


Fig. 1: Sites of HPV infection

Table 2: Sexually transmitted HPV types showing two categories (high- and low-risk)[8,9]

High-risk type	Cause cancer	Example: HPV 16 and 18
Low-risk type	Does not cause cancer; causes skin warts (condyloma acuminatum) on or around genitals and anus	Example: HPV 6 and 11

Flow Chart 1: Pathogenesis of HPV



PATHOGENESIS OF HPV

Worldwide, HPV has gained much attention in gynecological practice, being the casual factor of second most common cancer in females, i.e., cervical cancer [10] with majority cases (>85%) occurring in developing countries. The two most important hrHPV subtypes[11] (16 and 18) account for 70% of cervical cancer.

When a cell is infected with an oncogenic HPV strain, four steps are essential for progression into cervical cancer:

1. HPV transmission
2. Viral persistence
3. Progression of a clone of persistently infected cells to a precancerous lesion, finally
4. Invasion

With competent immune system clearance of HPV infection and regression of precancerous lesions, it can occur by cell-mediated immunity within 1–2 years of exposure (Flow Chart 1).[12,13]

SCREENING GUIDELINES

Over the past years, cervical cancer screening guidelines have undergone numerous important revisions by various major organizations. But, in 2012, all the major professional medical bodies [American Cancer Society (ACS)/American Society for Colposcopy and Cervical Pathology (ASCCP)/American Society for Clinical Pathology (ASCP)/American College of Obstetricians and Gynecologists (ACOG) and the United States Preventive Services Task Force (USPSTF)] have adopted comparable guidelines, hoping that uniformity in these guidelines will lead to consistent care through improved clinician as well as patient compliance (Table 3).

Table 3: ASCCP, ACS, ACOG, and ASCP guidelines

Age (years)	*Recommended screening*	*Comment*
Less than 21	No screening	
21–29	Pap smear alone every 3 years	
30–65	Pap smear and HPV co-testing every 5 years or Pap smear alone every 3 years	Screening by HPV testing alone is not recommended
65 and older	No screening after adequate negative prior screening results	Women with a history of high-grade Pap smear should continue age-based screening for at least 20 years
Women who have had hysterectomy	No screening necessary	Applies to women without a cervix and without a history of high-grade Pap smear or cancer in the past 20 years
Women vaccinated against HPV	Same as unvaccinated women	

Rationale for Revision in the Guidelines

- Females <21 years should not be screened because of extreme rarity of such cancer which is estimated to occur at 1–2 cases per million girls aged 15–19 years[14] because initiation in screening in <21 years has not shown a significant decrease in cervical cancer rates.[15,16]
- HPV co-testing in <30 years for screening purposes is not justified because it would largely detect transient HPV infections which is of no clinical significance because the incidence of cervical cancer is extremely low in this age group even when there is increased prevalence of hrHPV infection.[17]
- Co-testing should be used whenever available and is now the preferred screening method for women aged 35–60 years because it has achieved lower cancer rates with less screening and fewer follow-up colposcopy and cytology alone, which is highly suitable for developing countries like India, where cervical cancer ranks second among all the female cancers as well as there is high requirement for medical staff.[18]
- All bodies are in agreement that under usual circumstances, screening should be stopped at 65 years of age since the natural history of cervical cancer with preinvasive state is approximately 15–25 years after acquisition of HPV and therefore it is unlikely that a female who had not developed cytological abnormalities by 65 years of age will live long enough to develop cervical cancer.[19]

HUMAN PAPILLOMAVIRUS TESTING[20]

Since the initial HPV testing in 1999, it has been dominated by hybrid capture (HC2) technology and remains the most frequent and comparable standard HPV test. All are approved for use in reflex testing with atypical squamous cells of undetermined significance (ASC-US) cytology and in cotesting in women 30 years of age and older and grouped into the following four categories:

1. hrHPV DNA-based screening assays
2. hrHPV DNA-based screening assays with reflex or concurrent HPV 16, 18 genotype detection
3. hrHPV DNA-based genotyping assays
4. hrHPV E6/E7 messenger ribonucleic acid (mRNA) screening assays

hrHPV DNA-based screening assays

Test name: Qiagen HC2 and Cervista HPV HR test
Methodology: Both tests are *in vitro* DNA hybridization assay using a specific hrHPV RNA probe cocktail with signal amplification and qualitative chemiluminescence for detection of 13 hrHPV nucleic acids using a luminometer.

Besides this, Cervista HPV HR uses signal amplification method using fluorescent detection of hrHPV nucleic acids.

Both tests simply indicate the presence or absence of hrHPV types with no information regarding specific HPV types.

hrHPV DNA-based Screening Assays with Reflex or Concurrent HPV 16,18 Genotype Detection

Cervista HPV 16/18 test is a sister of Cervista HPV HR test and uses the same technology as the HPV HR test and allows qualitative fluorescent detection of types 16 and 18 DNA, therefore, approved by the Food and Drug Administration (FDA) to be used along with its sister test to determine the absence or presence of HPV 16/18.

hrHPV DNA-based Genotyping Assays

The FDA-approved test for HPV polymerase chain reaction (PCR) and DNA-based genotyping is the Cobas 4800 HPV test (Roche Molecular Diagnostics, Pleasanton, CA). This test uses real-time PCR methodology to amplify sequences fluorescently labeled for detection.

Result: The result can be reported in two ways:

1. As a pooled result with 14 targeted hrHPV types
2. Result for HPV 16 and 18 separately and a pooled result for other 12 high-risk types

hrHPV E6/E7 and mRNA Screening Assays

The Aptima HPV test (Hologic Gen-Probe, Inc San Diego, CA) is an FDA-approved hrHPV E6/E7 mRNA-based screening assay. The other testing modalities already discussed simply detect the presence of the virus without information on the integration of the virus into the host genome, a necessary step for a precancerous lesion. In this

sense, all those tests suffer from a diminished specificity for true disease. This transcription-mediated amplification-based assay allows detection of E6/E7 transcripts of 14 hrHPV types with no distinction between HPV types.

ROLE OF HPV TESTING IN CERVICAL CANCER

Global View

For the past 50 years, the conventional Papanicolaou along with more recently developed liquid-based cytology tests had been the preliminary tests for cervical cancer screening and with effective implementation of this cytology-based screening programs, cervical cancer rates have decreased by 50–90%.[21]

Rationale of Moving from PAP to HPV Testing for Cervical Cancer Screening

The HPV testing provides excellent negative predictive value because of high sensitivity as well as slow progression from incident infection to cancer.[22] Women who test hrHPV negative at one time point have 2-fold to 3-fold lower subsequent risk of cervical precancerous lesions and cancer compared with a negative cytology at any follow-up time. Reassurance from a single negative hrHPV test lasts longer than reassurance from a single negative cytology. Therefore, a negative HPV test safely permits longer intervals between screens than a negative cytology.

Cost-effectiveness of HPV Testing

Several health econometric studies have found the use of HPV testing in primary screening to be cost-effective after 30 years of age. A recent analysis focused on Europe found that, in most scenarios, HPV testing for primary cervical cancer screening every 5 years was more cost-effective than cytology every 5 years.[23]

CONCLUSION

Despite the success of cytology-based programs, cervical cancer remains the third most common female cancer and third most common cause of female cancer-related mortality globally, with an annual incidence of 530,000 and mortality of 275,000, respectively,[24] which can be explained by the fact that cervical cancer incidence and mortality are to be approximately 10-fold greater in low-income and middle-income countries (LMICs).

Most of the world's population in LMICs, having technical and financial barriers, making it difficult to implement cytology-based programs.[21,25] Therefore, it seems a foregone conclusion that one size does not fit all for cervical cancer screening. Thus, to address the global burden of cervical cancer, alternative prevention strategies should be adopted to reduce the mortality and incidence.

With lower resource settings comes the severe lack of healthcare infrastructure, including adequate medical records and only basic laboratory procedures, quality control measures, and safety precautions are usually not practiced. The improvement of laboratory structure requires significant financial and political investment.

Thus, relying only on cytology-based programs is not working in many countries and repeated cytology tests have resulted in decreased programmatic sensitivity. Hence, there is necessity of the robust and simplified HPV tests to be implemented for cancer prevention program. Various tests for lower resource setting are careHPV (Qiagen), a DNA test that detects the 13 carcinogenic HPV genotypes and HPV 66 in aggregate.[26]

The few changes that can result in early diagnosing and prevention are by coupling PCR-based test with self-collection that can minimize the costs, less screening, and allow high-volume screening.[27] Also setting up centralized testing offers the benefit of establishing and maintaining high-quality laboratories with requirement of good transport system and technology along with timely transmittal of test results to the clinicians for their follow-up and treatment. By uplifting and removing all the problems regarding the testing, including its feasibility, early diagnosing, and treatment can change the fate for incidence of the cervical cancer and, thus, reducing the risk for HPV.

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