TRAINEES GUIDELINES FOR CERVICAL CANCER SCREENING AT PRIMARY, SECONDARY AND TERTIARY LEVEL

GOVERNMENT OF MAHARASHTRA

MINISTRY OF HEALTH AND FAMILY WELFARE

TRAINEES GUIDELINES FOR CERVICAL CANCER SCREENING AT PRIMARY, SECONDARY AND TERTIARY LEVEL

I. Trainees

1. Primary Level:-
   - Medical officers
   - Nurses
   - ANM
   - ASHA
2. Secondary Level:-
   - ANM
   - Nurses
   - Medical officers
   - OBCY Specialists
3. Tertiary Level:-
   - ANM
   - Nurses
   - Medical officers
   - Undergraduates
   - Postgraduates
   - Interns
   - Consultants in OBGYN

II. Centre for training

As per Govt. of Maharashtra following centers are selected for training:-

1. District Hospital Wardha
2. MGIMS Sevagram, Wardha.
3. JNMC Sawangi (Meghe), Wardha

III. Resource Persons

1. MGIMS Sevagram:-

Prof.Poonam Varma Shivkumar, Prof & Head , Dept of OBGY
Dr Amardeep Tembere, Assistant Prof, Dept of OBGY
Dr.Shila Shelke, Assistant Prof, Dept of OBGY
Consultants in OBGY Dept.

2. JNMC Sawangi

Prof.Hariharan, Prof & Head , Dept of OBGY

Other Consultants in OBGY Dept.

3. **District Hospital Wardha**

   Civil surgeon

   Senior Medical Officer

   Specialist of OBGY

IV. Duration of training

It will be a training programme for **total 10(ten)** days.

Total number of trainees will be **54.**

Each Medical college will have **27** trainees.

Each centre will **divide 27 trainees** in **3 batches** consisting of **9 trainees each**.

V. Requirements for training

A. Infrastructure

1. **Accommodation:-** To be arranged and looked after by District Hospital
2. **Training Area:-** Conference Hall at the respective training centers.

B. Material and methods of training

Material

1. Trainee's guideline manual.
2. Power point presentations
3. Laptop and LCD with screen
4. Mannequins
5. Patients
6. Cervical Screening kits
7. Gloves
8. Stationary
9. Miscellaneous

Methods

1. Lectures
2. Demonstration and clinical exposure.
3. Symposiums
4. Direct Demonstration on patients
5. Group discussion
6. Hands on training

VI. Basic Needs

1. Food arrangement at training centre.
2. 2.Conveyance- Will be paid as per Govt.rules

CURRICULUM

I. ANATOMY OF CERVIX, TRANSFORMATION ZONE AND SQUAMOCOLUMNAR JUNCTION

In this session trainees will be taught regarding the basic and clinical anatomy of cervix including transformation zone, squamo-columnar junction, fornices and other surrounding structures. The aim is to make them understand the basic visual anatomy of the entire cervix so that trainees can differentiate the normal and abnormal anatomy of cervix . The emphasis will be given on clinic-pathological anatomy including vascular supply and lymphatic drainage of the cervix.

This session will be conducted by using power point presentations, mannequins and surgical video demonstrations.

Duration: - 2 hrs.

II. PHYSIOLOGY OF CERVIX

In this session the trainees will be taught the basic physiology of the cervix. The session will be directed towards the basic understanding the physiological and pathological changes on the cervix in various times. The various changes takes place in the cervix from prepubertal to pubertal stage, in various phases of menstruation, during pregnancy and peurperium, during perimenopausal and menopausal period and in old age will be taught.

The aim of this session will be to make trainees understand the various normal and physiological changes in the cervix and able to differentiate them from the pathological changes of the cervix.

This session will be conducted by using power point presentations, mannequins and surgical video demonstrations.

Duration: - 2 hrs.

III. PATHOGENESIS OF PREMALIGNANT AND MALIGNANT LESION

The session will be directed towards the basic pathogenesis of the premalignant and malignant lesion of the cervix. The emphasis will be given on understanding of the etiology and pathogenesis of cervical lesions. The causative factors of lesion will be informed and also the pathogenesis of cervical lesion including abnormal vascularity, metaplasia, dysplasia and carcinoma in situ lesions will be taught. The phase of initiation, progress and complications will be emphasized and made them understand the complication of the diseases.

The strategies for the prevention will be also taught during the session.

This session will be conducted by using power point presentations, picture demonstration, surgical video demonstrations and real case demonstrations.

Duration: 3 hrs.

IV. PATHOLOGY OF PREMALIGNANT AND MALIGNANT LESION – ABNORMAL CERVIX

In this session the trainee's will be taught regarding the pathology of the cervix. All the various types of premalignant and malignant lesions and their pathology will be taught. This will help them to understand the nature and type of the disease. The pathological aspect will also help them to understand what kind of investigations could be performed to diagnose the exact pathology.

This could be done with the help of power point presentations, picture demonstration, surgical video demonstrations and real case demonstrations.

Duration: 3 hrs.

V. BURDEN OF CERVICAL CANCER GLOBALLY AND IN INDIA WITH NEED FOR CERVICAL CANCER SCREENING

The trainees will be made familiar with the incidence, prevalence and global burden of the cancer cervix. The latest literature across the world and Indian population will be presented to them to understand the morbidity and mortality in the women. The correlation of the global burden and how it could be reduced by various screening tests will be told. Hence the importance of the screening programmes will be taught to them with relevance.

This could be done with the help of power point presentations

Duration:-1 hr

VI. CERVICAL SCREENING PROGRAMME-

1. PURPOSE
   Why these screening tests are performed and how these tests will help the women to prevent the cancer screening.

2. ON WHOM IT IS DONE
   The potential candidates for the cancer screening will be selected. The age group and high risk population will be selected according to selection criteria.

3. MATERIALS NEEDED

- Health Education material like Posters, Handouts, Guideline booklets
- Surgical Instruments:-Sim's Speculum, Anterior vaginal wall retractor , Biopsy forceps etc.
- Ayre's spatula, Brush Cytology material.

- Slides, box for sending smear
- Gloves, Dressing materials
- Chemicals eg.90 % Alcohol, Acetic acid, Lugol's Iodine, normal saline
- Colposcope, Magnoscope.

4. HOW AND WHEN TO DO? METHODOLOGIES – PAP SMEAR, VIA, VILI, VIAM, COLPOSCOPY, LIQUID BASED CERVICAL CYTOLOGY WITH HPV TESTING

   In this session the trainees' will be taught how to perform various screening tests. With the help of various teaching tools the trainees' will be made to understand how to perform various screening tests in the selected women and how to interpret them.

   This could be done with the help of power point presentations, picture demonstration, surgical video demonstrations and real case demonstrations.

   Duration: 3hrs.

5. PRECAUTIONS TO BE TAKEN

   In this session the trainees' will be taught how to take necessary precaution while performing the screening tests. Necessary skills will be discussed so that the procedures will be performed exactly in the way as guided in the manual so that the interpretation should not be hampered and there should be no inter observer difference in the procedure performed and its interpretation.

   Trainees' will also be educated regarding the universal precaution techniques while performing the tests.

   This could be done with the help of power point presentations and picture demonstration

   Duration: 1 hr

6. INTERPRETATION

   The trainee's will be made understand how to interpret the results of various tests performed. The criteria's for the interpretation will be discussed.

   This could be done with the help of power point presentations, picture demonstration, video demonstrations and real case demonstrations.

   In this session the trainees' will be assessed by mock assessment tests.

   Duration: - 2 hrs.

7. FOLLOW UPS

The trainee's will be taught regarding the follow up for the women with respect to the various screening tests. A definite follow up plan will be make out for each screening test and they will be taught regarding the counseling and follow up for the next visits.

The immediate and subsequent follow up will be discussed and at which level women has to visit will also be discussed.

This session will be done with the help of power point presentation.

Duration: 1 hr

8. WHEN TO REPEAT

The trainee's will be made understand to chalk out the follow up test and repeat tests depending on the results of the screening tests. How to guide women for repeat tests will be taught and how to individualized plan for the particular women will be discussed.

This session will be done with the help of power point presentation.

Duration: 1 hr

9. DOWNSTAGING AND ITS RELEVANCE

This is the important step which trainee's will be taught how to train paramedical staff about abnormal cervix and how to refer these women to appropriate centre. The group discussion will be conducted on the importance of detecting cancer cervix in early stages so the better treatment can be planned and quality management can be done

Group discussion, video of cervical abnormalities

Duration :1 hr

10. HEALTH EDUCATION - KNOWLEDGE AND INFORMATION TO BE GIVEN TO WOMEN

The trainees' have to educate and teach women of general population and in the high risk group regarding the health education and awareness of the cancer cervix. The aim of this session is to enable trainee's to give effective health education regarding the health practices, high risk behavior, adolescent and family life education, genital infections, health and hygiene and many other aspects of cancer cervix.

This could be done with the help of power point presentations, picture demonstration, health education pamphlets, posters etc.

Duration: 3hrs.

11. WHEN AND WHERE TO REFER THE WOMEN HAVING ABNORMAL SCREENING/ VISUAL SIGNS WITH REFERRAL DETAILS

On finding of the abnormal results of the screening tests, the trainees' should be able to guide the women for proper referral from primary to secondary and from secondary to tertiary care centers for necessary follow up. The trainee's will be taught for the need and importance of the necessary referral with the proper referral details. The predeveloped referral format will be discussed with them and its implementation strategy will be discussed.

This session will be discussed with the help of predeveloped referral format, clinical assessment tools and format.

12. FOLLOW UP OF REFERRED WOMEN

The trainees' will be educated for the follow up of the women on individualized basis. The format for the follow up for the particular disease will be developed trainees will be trained for the follow up. At each level the follow up programme will be developed and necessary training for the follow up will be given to the trainee's at all levels.

Schedule for the Training of the trainees for cancer cervical screening programme.

I. Day 1:-

Welcome and inauguration.

Introduction to the training programme.

Pre course questionnaire

1. Lecture: Anatomy of the cervix: 1hr
2. Demonstration on the model:- 1 hr.
3. Physiology of the cervix:- 1 hr
4. Demonstration on the model: 1 hr

II. Day 2:-

1. Lecture:-Pathogenesis of the premalignant and malignant lesion of the cervix:-1hr
2. Demonstration on the models and video presentation:- 2 hr

III. Day 3

1. Lecture:-Pathology of the premalignant and malignant lesion of the cervix
2. Demonstration on the models, pictures and power point presentations.

IV. Day 4

1. Lecture: - Power presentation on Burden of cervical cancer globally and in India with need for cervical cancer screening.
2. Lecture 2:- introduction to Cervical screening programme.

V. Day 5

Lecture on Cervical screening programme

VI. Day 6

Down staging and its relevance.
Video demonstration.
Practical demonstration on manniquines.
Practical demonstration on the patients.

VII. Day7

Health education to the women

Counseling

Disease information

Importance of early screening

VIII. Day 8

Referral system
When, How, Where to refer.
Follow up programme for the screening programme at various levels.

IX. Day 9

Evaluation and assessment of the trainees'

Post test questionnaire and practical demonstration on the mannequins.

X. Day 10

1. Revision of the course
2. Discussion of the important topics.
3. Practical tips for screening.
4. Take home message.

LITERATURE REVIEW

ANATOMY :

• The cervix, the lower fibromuscular portion of the uterus, measures 3-4 cm in length and 2.5 cm in diameter; however, it varies in size and shape depending on age, parity and menstrual status of the woman.

• Ectocervix is the most readily visible portion of the cervix; endocervix is largely invisible and lies proximal to the external os.

• Ectocervix is covered by a pink stratified squamous epithelium, consisting of multiple layers of cells and a reddish columnar epithelium consisting of a single layer of cells lines the endocervix. The intermediate and superficial cell layers of the squamous epithelium contain glycogen.

• The location of squamocolumnar junction in relation to the external os varies depending upon age,menstrual status, and other factors such as pregnancy and oral contraceptive use.

• Squamous metaplasia in the cervix refers to the physiological replacement of the everted columnar epithelium on the ectocervix by a newly formed squamous epithelium from the subcolumnar reserve cells.

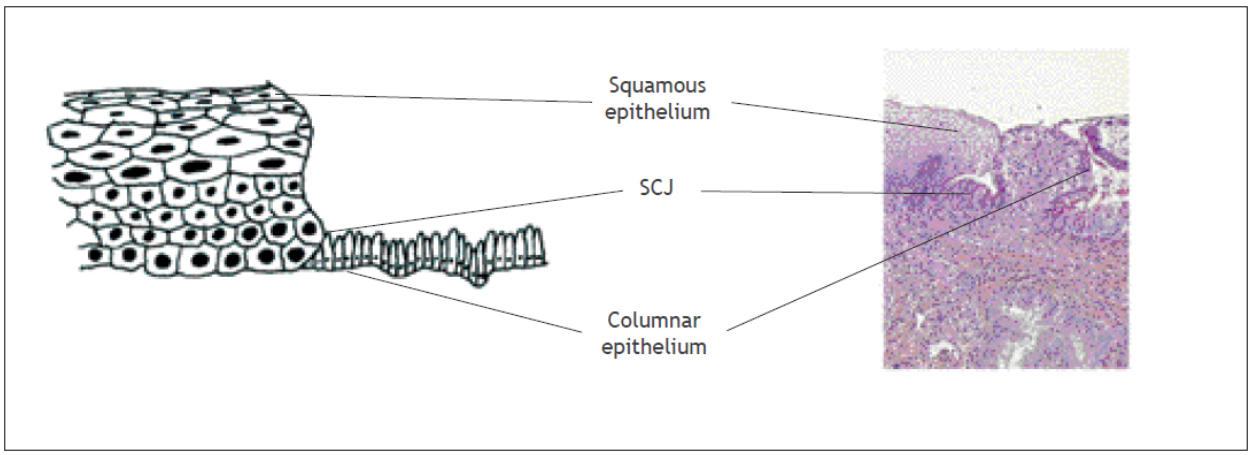
• The region of the cervix where squamous metaplasia occurs between the original and new squamo-columnar junction is referred to as the transformation zone.

• Identifying the transformation zone is of great importance in colposcopy, as almost all manifestations of cervical carcinogenesis occur in this zone.

Squamocolumnar junction

The squamocolumnar junction appears as a sharp line with a step, due to the difference in the height of the squamous and columnar epithelium. The location of the squamocolumnar junction in relation to the external os is variable over a woman's lifetime and depends upon factors such as age, hormonal status, birth trauma, oral contraceptive use and certain physiological conditions such as pregnancy. The squamocolumnar junction visible during childhood, perimenarche, after puberty and early reproductive period is referred to as the original squamocolumnar junction, as this represents the junction between the columnar epithelium and the 'original' squamous epithelium laid down during embryogenesis and intrauterine life. During childhood and perimenarche, the original squamocolumnar junction is located at, or very close to, the external os . After puberty and during the reproductive period, the female genital organs grow under the influence of estrogen. Thus, the cervix swells and enlarges and the endocervical canal elongates. This leads to the eversion of the columnar epithelium of the lower part of the

endocervical canal on to the ectocervix . This condition is called ectropion or ectopy, which is visible as a strikingly reddish-looking ectocervix on visual inspection.



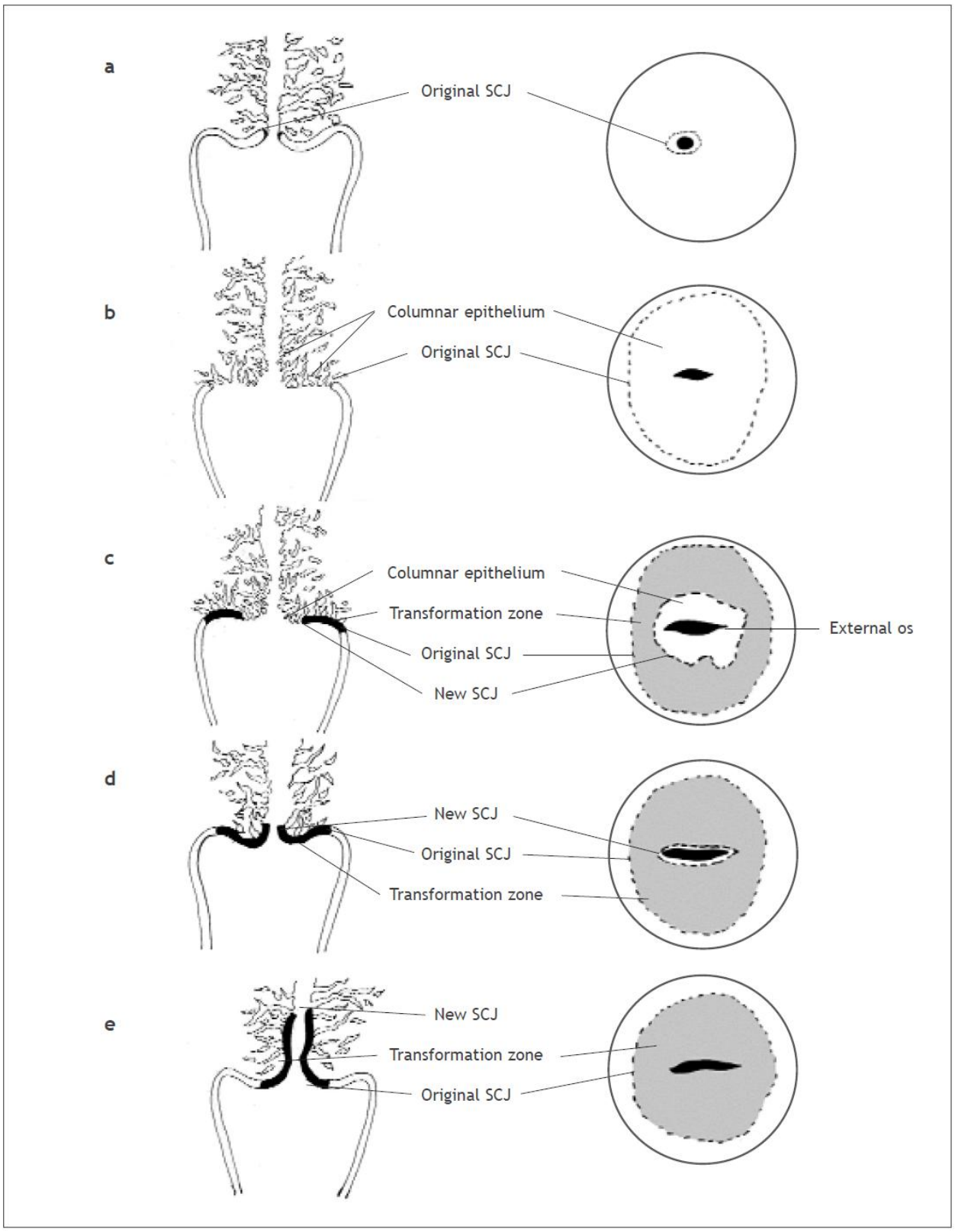


FIGURE 1.7: Location of the squamocolumnar junction (SCJ) and transformation zone; (a) before menarche; (b) after puberty and at early reproductive age; (c) in a woman in her 30s; (d) in a perimenopausal woman; (e) in a postmenopausal woman

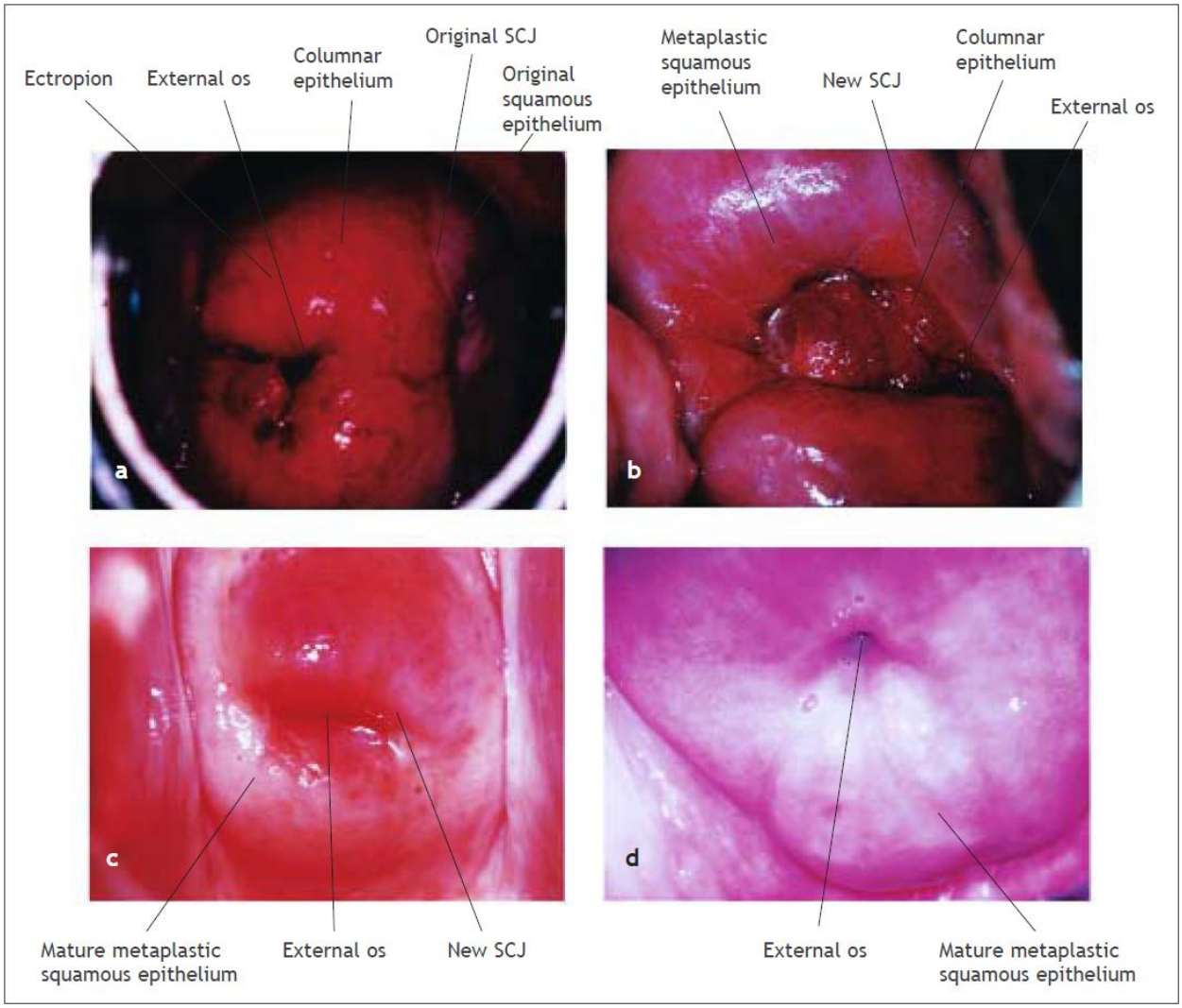


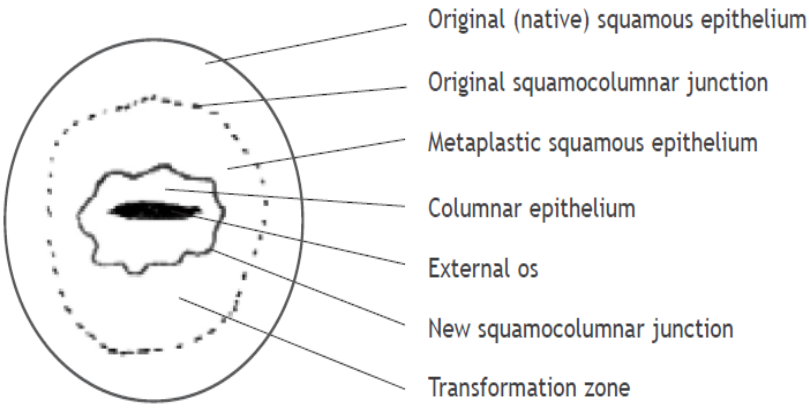
FIGURE : Location of squamocolumnar junction (SCJ)

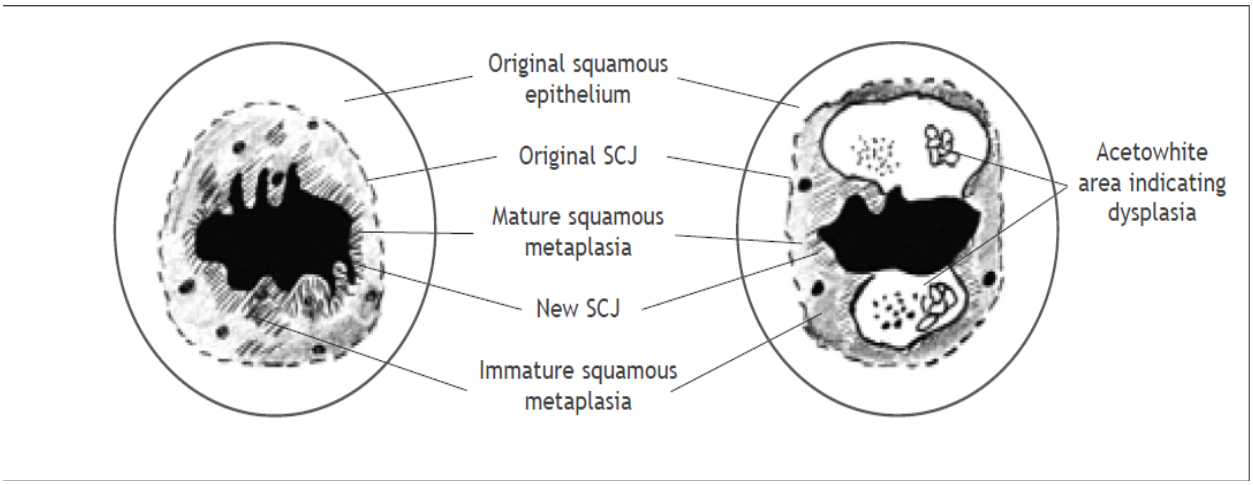
(a) Original squamocolumnar junction (SCJ) in a young woman in the early reproductive age group. The SCJ is located far away from the external os. Note the presence of everted columnar epithelium occupying a large portion of the ectocervix producing ectropion

(b) The new SCJ has moved much closer to the external os in a woman in her 30s. The SCJ is visible as a distinct white line after the application of 5% acetic acid due to the presence of immature squamous metaplastic epithelium adjacent to the new SCJ

(c) The new SCJ is at the external os in a perimenopausal woman

(d) The new SCJ is not visible and has receded into the endocervix in a postmenopausal woman. Mature metaplastic squamous epithelium occupies most of the ectocervix


Original (native) squamous epithelium
Original squamocolumnar junction
Metaplastic squamous epithelium
Columnar epithelium
External os
New squamocolumnar junction
Transformation zone



Squamous metaplasia

The physiological replacement of the everted columnar epithelium by a newly formed squamous epithelium is called squamous metaplasia. The vaginal environment is acidic during the reproductive years and during pregnancy. The acidity is thought to play a role in squamous metaplasia. When the cells are repeatedly destroyed by vaginal acidity in the columnar epithelium in an area of ectropion, they are eventually replaced by a newly formed metaplastic epithelium. The irritation of exposed columnar epithelium by the acidic vaginal environment results in the appearance of sub-columnar reserve cells. These cells proliferate producing a reserve cell hyperplasia and eventually form the metaplastic squamous epithelium. As already indicated, the metaplastic process requires the appearance of undifferentiated, cuboidal, sub-columnar cells called reserve cells , for the metaplastic squamous epithelium is produced from the multiplication and differentiation of these cells. These eventually lift off the persistent columnar epithelium . The exact origin of the reserve cells is not known, though it is widely believed that it develops from the columnar epithelium, in response to irritation by the vaginal acidity. The first sign of squamous metaplasia is the appearance and proliferation of reserve cells . This is initially seen as a single layer of small, round cells with darkly staining nuclei, situated very close to the nuclei of columnar cells, which further proliferate to produce a reserve cell hyperplasia. Morphologically, the reserve cells have a similar appearance to the basal cells of the original squamous epithelium, with round nuclei and little cytoplasm. As the metaplastic process progresses, the reserve cells proliferate and differentiate to form a thin, multicellular epithelium of immature squamous cells with no evidence of stratification . The term immature squamous metaplastic epithelium is applied when there is little or no stratification in this thin newly formed metaplastic epithelium. The cells in the immature squamous metaplastic epithelium do not produce glycogen and, hence, do not stain brown or black with Lugol's iodine solution. Groups of mucin-containing columnar cells may be seen embedded in the immature squamous metaplastic epithelium at this stage. Numerous continuous and/or isolated fields or foci of

immature squamous metaplasia may arise at the same time. It has been proposed that the basement membrane of the original columnar epithelium dissolves and is reformed between the proliferating and differentiating reserve cells and the cervical stroma. Squamous metaplasia usually begins at the original squamocolumnar junction at the distal limit of the ectopy, but it may also occur in the columnar epithelium close to this junction or as islands scattered in the exposed columnar epithelium. As the process continues, the immature metaplastic squamous cells differentiate into mature stratified metaplastic epithelium . For all practical purposes, the latter resembles the original stratified squamous epithelium. Some residual columnar cells or vacuoles of mucus are seen in the mature squamous metaplastic epithelium, which contains glycogen from the intermediate cell layer onwards. Thus, it stains brown or black after application of Lugol's iodine. Several cysts, called nabothian cysts (follicles), may be observed in the mature metaplastic squamous epithelium . Nabothian cysts are retention cysts that develop as a result of the occlusion of an endocervical crypt opening or outlet by the overlying metaplastic squamous epithelium . The buried columnar epithelium continues to secrete mucus, which eventually fills and distends the cyst. The entrapped mucus gives an ivory-white to yellowish hue to the cyst on visual examination . The columnar epithelium in the wall of the cyst is flattened and ultimately destroyed by the pressure of the mucus in it. The outlets of the crypts of columnar epithelium, not yet covered by the metaplastic epithelium, remain as persistent crypt openings. The farthest extent of the metaplastic epithelium onto the ectocervix can be best judged by the location of the crypt opening farthest away from the squamocolumnar junction. Squamous metaplasia is an irreversible process; the transformed epithelium (now squamous in character) cannot revert to columnar epithelium.Squamous metaplasia may progress at varying rates in different areas of the same cervix, and hence many areas of widely differing maturity may be seen in the metaplastic squamous epithelium with or without islands of columnar epithelium. The metaplastic epithelium adjacent to the squamocolumnar junction is composed of immature metaplasia, and the mature metaplastic epithelium is found near the original squamocolumnar junction. Further development of the newly formed immature metaplastic epithelium may take two directions . In the vast majority of women, it develops into a mature squamous metaplastic epithelium, which is similar to the normal glycogen containing original squamous epithelium for all practical purposes. In a very small minority of women, an atypical, dysplastic epithelium may develop. Certain oncogenic human papillomavirus (HPV) types may persistently infect the immature basal squamous metaplastic cells and transform them into atypical cells with nuclear and cytoplasmic abnormalities. The uncontrolled proliferation and expansion of these atypical cells may lead to the formation of an abnormal dysplastic epithelium which may regress to normal, persist as dysplasia or progress into invasive cancer after several years.

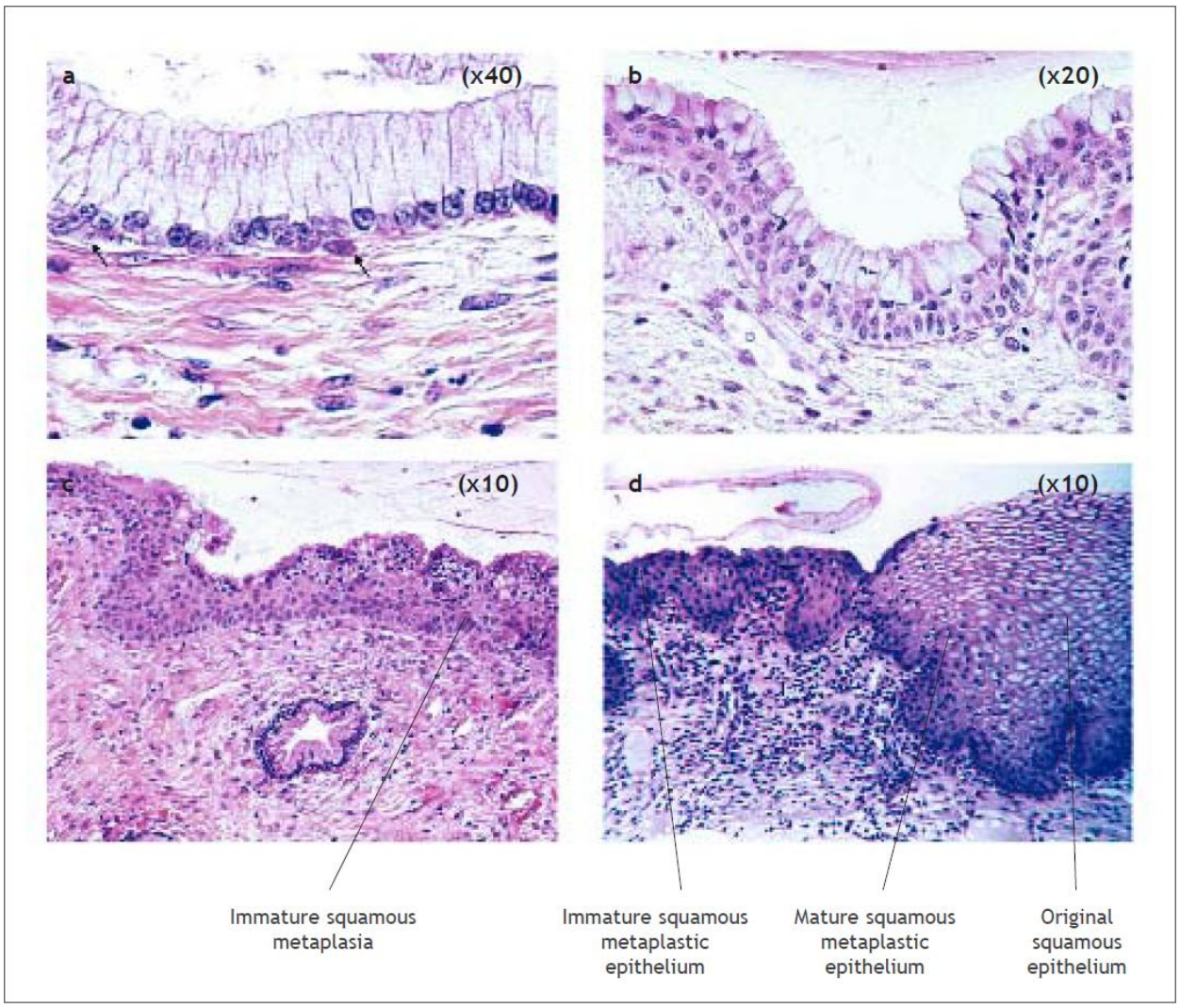


FIGURE 1.9: Development of squamous metaplastic epithelium

(a) The arrows indicate the appearance of the subcolumnar reserve cells

(b) The reserve cells proliferate to form two layers of reserve cell hyperplasia beneath the overlying layer of columnar epithelium

(c) The reserve cells further proliferate and differentiate to form immature squamous metaplastic epithelium. There is no evidence of glycogen production

(d) Mature squamous metaplastic epithelium is indistinguishable from the original squamous epithelium for all practical purposes.

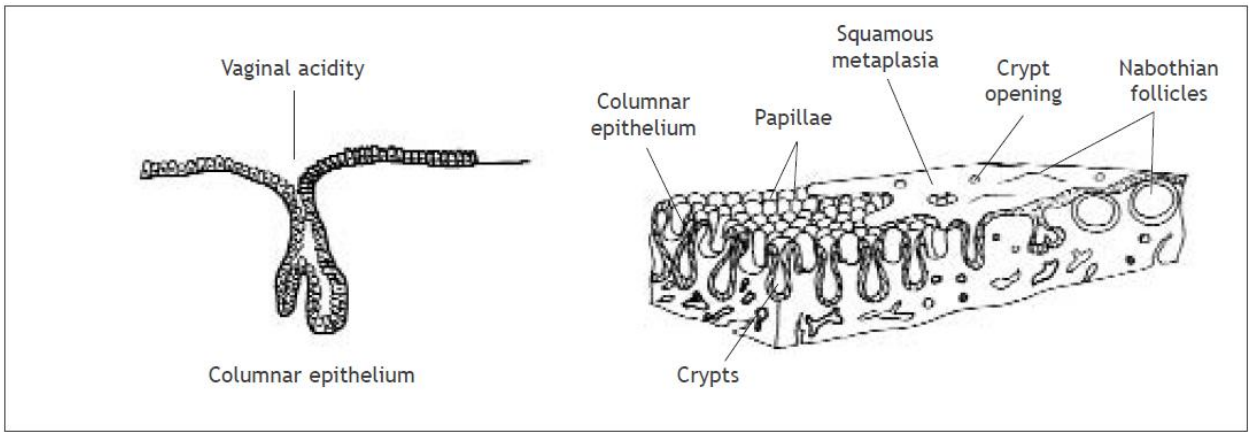


FIGURE 1.10: Squamous metaplastic epithelium covering the crypt openings, leading to the formation of nabothian retention cysts

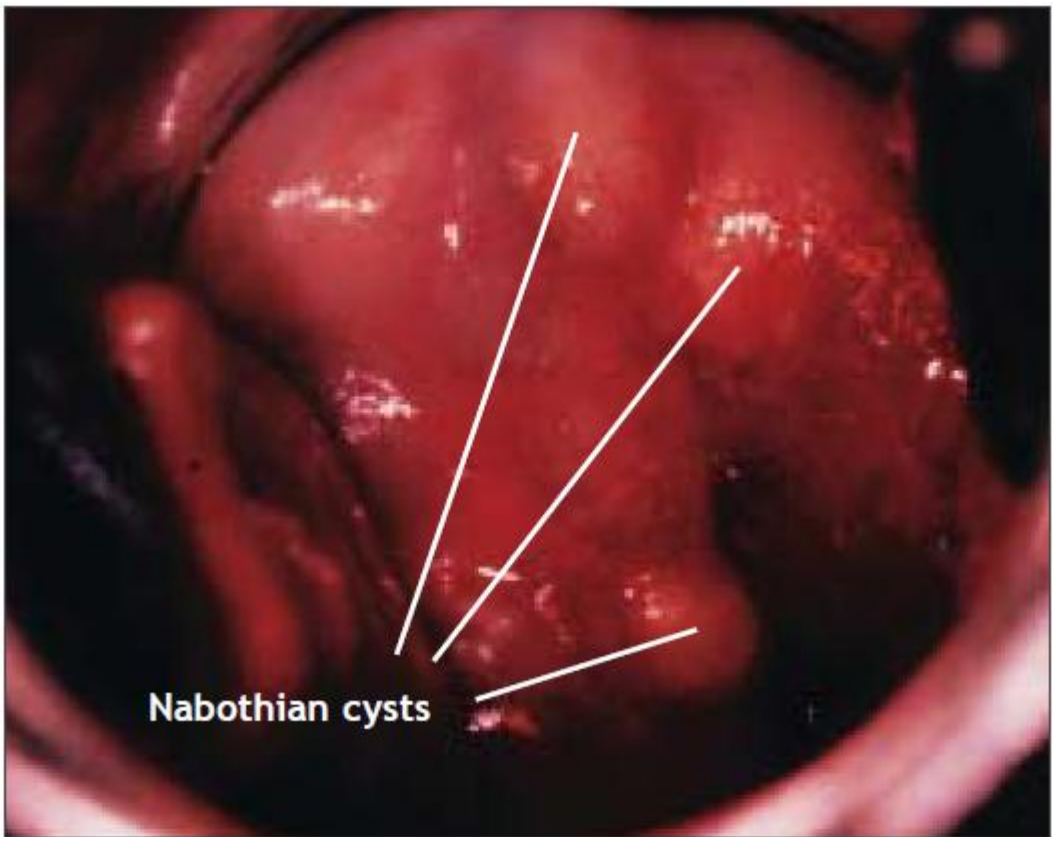
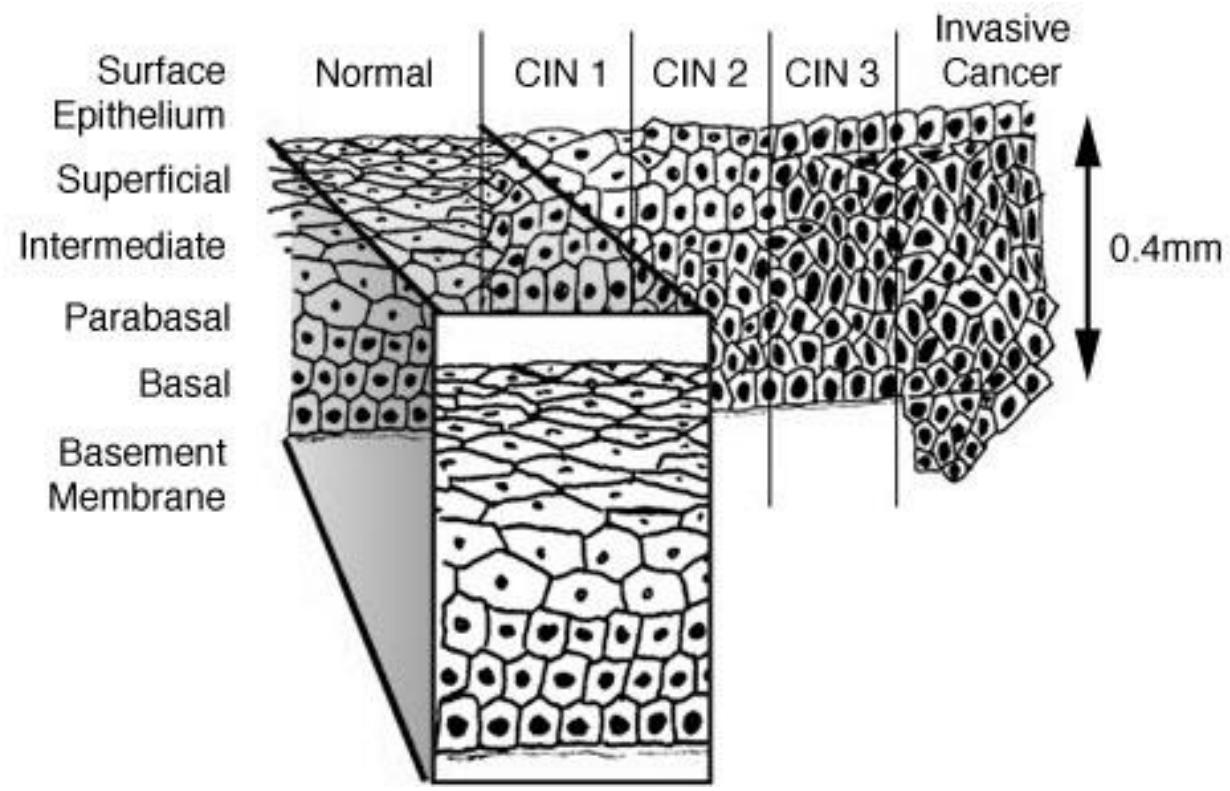


FIGURE 1.11: Multiple nabothian cysts in the mature squamous metaplastic epithelium occupying the ectocervix.



What is Cervical Cancer?

Cancer refers to a class of diseases in which a cell or a group of cells divide and replicate uncontrollably, intrude into adjacent cells and tissues (invasion) and ultimately spread to other parts of the body than the location at which they arose (metastasis) (National Cancer Institute 2009).

In cervical cancer, (cancer of the uterine cervix), cancer develops in the tissues of the cervix, which is a part of the female reproductive system. The cervix connects the upper body of the uterus to the vagina. The endocervix (the upper part which is close to the uterus) is covered by glandular cells, and the ectocervix (the lower part which is close to the vagina) is covered by squamous cells. The transformation zone refers to the place where these two regions of the cervix meet (American Cancer Society 2009). There are several types of cervical cancer, classified on the basis of where they develop in the cervix. Cancer that develops in the ectocervix is called squamous cell carcinoma, and around 80- 90% of cervical cancer cases (more than 90% in India) are of this type [WHO/ICO Information Centre on HPV and Cervical Cancer (a)]. Cancer that develops in the endocervix is called adenocarcinoma. In addition, a small percentage of cervical cancer cases are mixed versions of the above two,

and are called adenosquamous carcinomas or mixed carcinomas. There are also some very rare types of cervical cancer, such as small cell carcinoma, neuroendocrine carcinoma etc. (American Cancer Society). The rest of this factsheet will focus on the first two types, as they constitute the greatest burden, globally as well as in India.

Distribution, prevalence and incidence of Cervical Cancer in India

Prevalence/Incidence of Cervical Cancer As of 2002, the 1 year prevalence of cervical cancer in India was 101,583, and the 5 year prevalence was 370,243, accounting for approximately 26% of global prevalence, and 83% of total prevalence in South Central Asia* (GLOBACAN 2002 database, IARC). In India, the age-adjusted incidence of cervical cancer (30.7 per 100,000 women, 132,082 incident cases) is the highest relative to that of all other types of cancer, and is higher than the average for the South Central Asia region (GLOBACAN 2002 database, IARC 2009). By 2025, the number of new cervical cancer cases in India is projected to increase to 226,084 [WHO/ICO Information Centre on HPV and Cervical Cancer (a)]. Cervical cancer is the leading cancer among women in terms of incidence rates in 2 out of the 12 Population Based Cancer Registries (PBCRs) in India, and has the second highest incidence rate after breast cancer in the rest of the PBCRs (table 1, National Cancer Registry Programme and World Health Organisation). The age-adjusted incidence is highest in Chennai, a metropolitan city in the south, and lowest in Thiruvanathapuram, the capital of Kerela (National Cancer Registry Programme and World Health Organisation). There is a high incidence belt in the north eastern districts of Tamil Nadu, as well as in two districts in the North-Eastern region of the country

Burden of Cervical Cancer in India

India has a disproportionately high burden of cervical cancer (Shanta et al, 2000). Although its age standardized death rate of 9.5 deaths per 100,000 population is representative of global rates, it accounts for nearly one-third of global cervical cancer deaths (WHO 2009b, GLOBOCAN 2002, IARC 2009). There is considerable excess mortality from cervical cancer in India relative to the world, and the South Asia region. (National Cancer Registry Programme 2009, WHO 2004). Cervical cancer is the third largest cause of cancer mortality in India after cancers of the mouth & oropharynx, and oesophagus, accounting for nearly 10% of all cancer related deaths in the country (WHO, 2009b). Among women, it is the leading cause of cancer mortality, accounting for 26% of all cancer deaths (GLOBOCAN 2002, IARC 2009). According to IARC estimates, mortality from cervical cancer is expected to witness a 79% increase from 74,118 deaths in 2002 to 132,745 deaths by 2025 (National Cancer Registry Programme 2009, WHO 2004). Another measure of disease burden is Disability Adjusted Life Years (DALYs). At a rate of 113 age-adjusted DALYs per 100,000 population, cervical cancer accounts for 26.5% of global cervical cancer DALYs, and 11.6% of total cancer DALYs in India (WHO 2009b).

In 2004, cervical cancer was the 5th most common cause of cancer death among women in the world, and had:

• 489,000 new cases

• An age-standardised incidence rate (global) of 16 per 100,000 women in 2002

• 1-year prevalence of 381,033, and 5-year prevalence of 1.41 million in 2002

• 268,000 deaths (3.6% out of 7.4 million cancer deaths)

• 9 age-standardized deaths per 100,000 in 2002

• 3,719,000 DALYs (disability adjusted life-years)

Cervical Cancer Burden in India

In 2004, cervical cancer was the third largest cause of cancer mortality in India, and had:

• An age-standardised incidence rate of 30.7 per 100,000 women in 2002

• 1-year prevalence of 101,583, and 5-year prevalence of 370,243 in 2002

• 72,600 deaths (nearly 10% out of 729,600 cancer deaths)

• 6.5 deaths per 100,000

• 9.5 age-standardized deaths per 100,000

• 987,000 DALYs

• 88 DALYs per 100,000

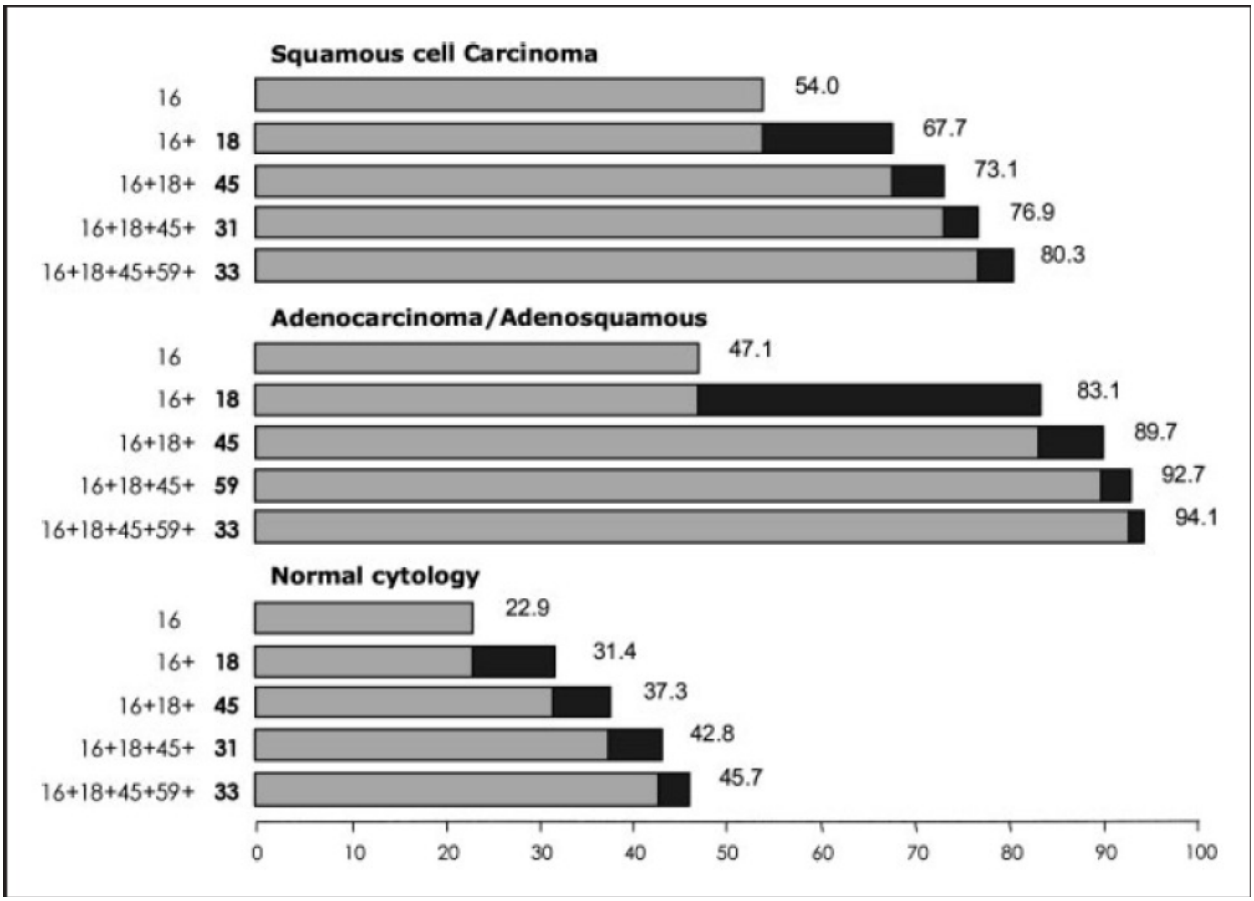
• 113 age-adjusted DALYs per 100,000

(WHO, 2009b; GLOBOCAN 2002 database, IARC)

Risk Factors for Cervical Cancer

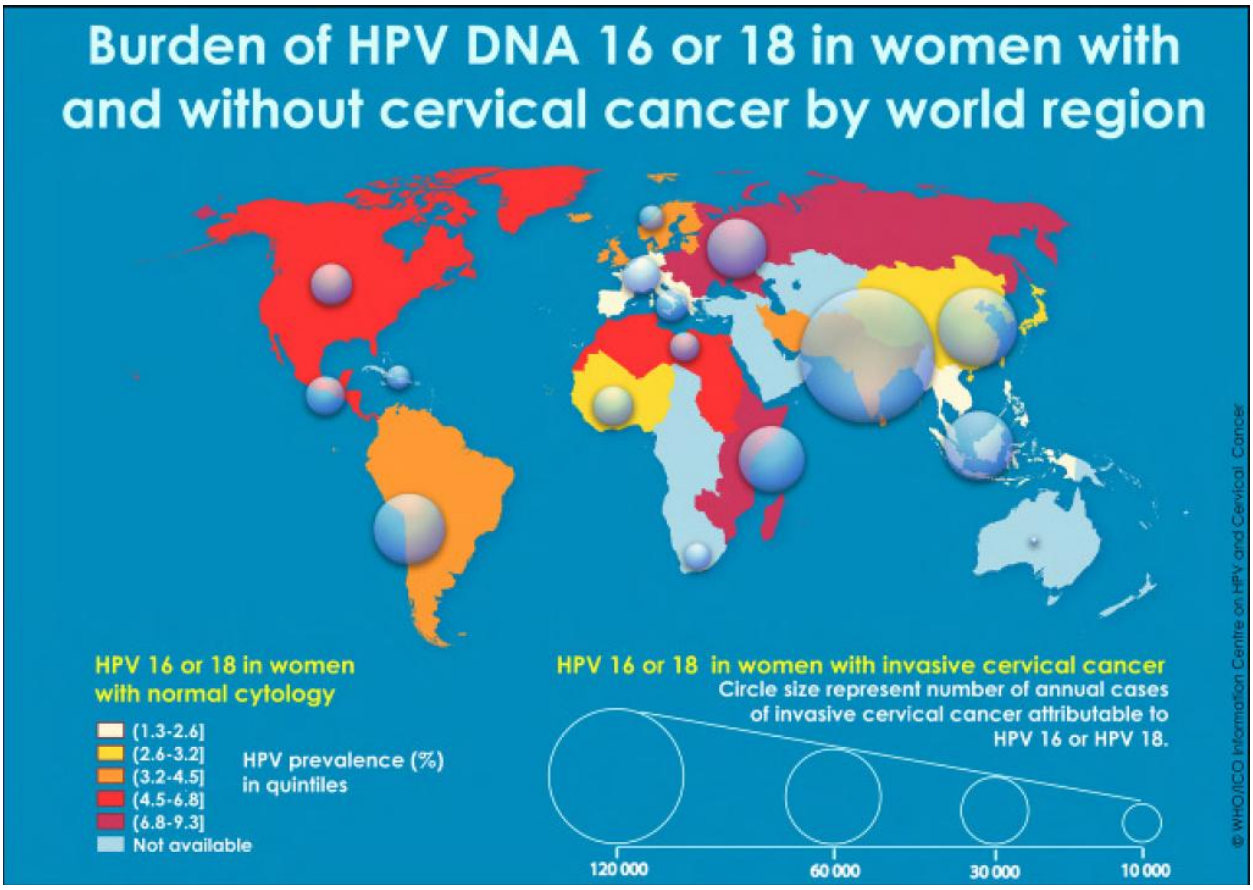
The main risk factor for the development of cervical cancer is human papilloma virus (HPV) infection, DNA of which has been found in almost all cases of invasive cervical cancer (Bosch and de Sanjosé, 2003). HPV is a sexually transmitted infection, making cervical cancer a chronic disease with an infectious etiology (Alliance for Cervical Cancer Prevention, Cancer Research UK). At least 50% of sexually active men and women get HPV at some point in their lives [Centers for Disease Control and Prevention (c)]. Most women with HPV infection will not develop cancer, and the infection usually resolves spontaneously; however, around 3-10% of women with HPV develop persistent infections, and are at high risk of developing cervical cancer (Monsonego et al, 2004). Although there are several strains of HPV infection, (most of which have been found to increase the risk of developing cervical cancer) two strains: HPV 16 and 18, account for more than 70% of all cervical cancer cases; five other strains: HPV 31, 33, 35, 45, 52 and 58 account for an additional 20% of cases [WHO/ICO Information Centre on Human Papilloma Virus and Cervical Cancer (a); Bosch and de Sanjosé, 2003]. While in squamous cell carcinoma, HPV 16 seems to predominate, HPV 18 seems to play an equally important role in adenocarcinoma (figure 5, Bosch and de Sanjosé, 2003).

Cumulative prevalence of common HPV types in women with squamous cell carcinoma, adenocarcinoma, and normal cytology .



Global prevalence of HPV infection in the general female population is estimated at 11.4% (95% CI 11.3, 11.5) [WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (a)]. However, prevalence varies greatly from country to country, ranging from 2% in South Vietnam to 43% in Zimbabwe (Bosch and de Sanjosé, 2003). In India, prevalence of HPV infection is 7.9% (7.5-8.2), lower than the world average [WHO/ICO Information Centre on Human Papilloma Virus and Cervical Cancer (a)]. Despite this, the absolute number of cases of invasive cervical cancer attributable to HPV infection is highest in the South Asia region [figure 6, WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (b)].

Burden of HPV DNA 16/18 in women with and without cervical cancer by world region



The prevalence of HPV DNA is much higher in individuals with invasive cancer than in those with normal cytology (National Cancer Registry Programme 2009, World Health Organization 2004), and the odds ratios (OR) associated with HPV infection and cervical cancer are among the highest observed in any disease (Bosch and de Sanjosé, 2003). The IARC multicentre case-control study found an OR of 158.2 (95% CI 113.4, 220.6) for squamous cell cervical cancer among cases (with any HPV infection) relative to controls, with the highest OR for HPV 16 infection (434.5 [278.2– 678.7]), and the lowest OR for HPV 6 infection (4.3 [0.5–38.4]) (Muñoz et al, 2003).

However, there is considerable regional and between-country variation in this association, with HPV 16/18 prevalence in invasive cervical cancer cases ranging from 65% in South/Central America to 76% in North America (Smith et al, 2007). In India, prevalence of HPV 16/18 in invasive cervical cancer cases is 82.5% (95% CI 9.5, 85.1) (National Cancer Registry Programme and World Health Organisation). A case-control study conducted in Chennai, India, found an almost 500 fold increase in the odds of having cervical carcinoma in cases with any HPV infection relative to controls with no HPV infection (figure 7) (Francheschi et al, 2003).

Odds of having cervical cancer among individuals with HPV infection relative to those without, in Chennai, India

	Cervical carcinoma		Controls		OR (95% CI)[2]
	No.	(%)	No.	(%)	
HPV					
Negative	1	(0.5)	133	(72.3)	1[3]
Positive (any type)	190	(99.5)	51	(27.7)	497.9 (67.7–999)
Multiple infection					
No	160	(83.8)	44	(23.9)	1[3]
Yes	30	(15.7)	7	(3.8)	1.2 (0.5–3.0)
HPV type(s)					
HPV 16	115	(60.2)	32	(17.4)	1[3]
HPV 18	28	(14.7)	2	(1.1)	3.9 (0.9–17.4)
HPV 16 and HPV18	5	(2.6)	2	(1.1)	0.7 (0.1–3.8)
HPV 16-associated types[4]	25	(13.1)	1	(0.5)	7.1 (0.9–54.4)
HPV 18-associated types[5]	8	(4.2)	4	(2.2)	0.6 (0.2–2.0)
Other types	9	(4.7)	10	(5.4)	0.3 (0.1–0.7)

OR, odds ratio; CI, confidence interval; HPV, human papillomavirus.–[1]HPV information was not available for 14 cases and 29 controls.–[2]Estimates from unconditional logistic regression equations including terms for age and area of residence.–[3]Reference category.–[4]HPV 31, 33, 35, 52 and 58, in absence of HPV 16 and 18.–[5]HPV 39, 45, 59 and 68, in absence of HPV 16 and 18.

The level of sexual activity of a person will affect the risk of acquiring HPV infection. Early age of first intercourse, multiple sexual partners, unprotected sex and sex with uncircumcised men, have been found to increase the risk of contracting HPV infection (figure 9) (Francheschi et al, 2003; World Health Organisation, 2006; Biswas et al, 1997). For example, having more than 3 sexual partners during a woman's lifetime will increase the risk of cervical cancer by 94% compared to women with one lifetime partner (figure 8). Among men, high lifetime number of sexual partners [multivariate OR for 2-9 partners relative to none 2.11 (1.17-3.78)] and recent number of sexual partners [multivariate OR for 2 partners in 3 months relative to none 2.09 (1.25-3.49)] have been found to increase the risk of contracting HPV infection, while not having had sex in the past 3 months [multivariate OR 0.42 (0.22-0.81)] and circumcision [multivariate OR 0.70 (0.52-0.94)] have been found to have a protective effect (Giuliano et al, 2009).
There are additional factors that increase the risk of developing cervical cancer after contracting HPV infection. These include smoking, oral contraceptive use, high parity, and infection with other sexually transmitted diseases such as HIV, Herpes, Chlamydia, gonorrhoea, and syphilis (de González et al, 2004; Plummer et al, 2003; Moreno et al, 2002; International Collaboration of Epidemiological Studies of Cervical Cancer, 2007; Smith et al, 2003; Muñoz et al, 2002) (figure 9, de González et al, 2004).

What are the key statistics about cervical cancer?

The American Cancer Society's estimates for cervical cancer in the United States are for

2013:

• About 12,340 new cases of invasive cervical cancer will be diagnosed.

• About 4,030 women will die from cervical cancer.

Some researchers estimate that non-invasive cervical cancer (carcinoma in situ) occurs about 4 times more often than invasive cervical cancer. Cervical cancer was once one of the most

common causes of cancer death for American women. Then, between 1955 and 1992, the cervical cancer death rate declined by almost 70%. The main reason for this change was the increased use of the Pap test. This screening procedure can find changes in the cervix before cancer develops. It can also find cervical cancer early − in its most curable stage. The death rate from cervical cancer has been stable in recent years. Cervical cancer tends to occur in midlife. Most cases are found in women younger than 50. It rarely develops in women younger than 20. Many older women do not realize that the risk of developing cervical cancer is still present as they age. More than 20% of cases of cervical cancer are found in women over 65. However these cancers rarely occur in women who have been getting regular tests to screen for cervical cancer before they were 65.

A risk factor is anything that changes your chance of getting a disease such as cancer.

Different cancers have different risk factors.

Cervical cancer risk factors include:

1. Human papilloma virus infection

The most important risk factor for cervical cancer is infection by the human papilloma virus (HPV). HPV is a group of more than 150 related viruses, some of which cause a type of growth called a papilloma, which are more commonly known as warts. HPV can infect cells on the surface of the skin, and those lining the genitals, anus, mouth and throat, but not the blood or internal organs such as the heart or lungs. HPV can be passed from one person to another during skin-to-skin contact. One way HPV is spread is through sex, including vaginal and anal intercourse and even oral sex. Different types of HPVs cause warts on different parts of the body. Some cause common warts on the hands and feet; others tend to cause warts on the lips or tongue. Certain types of HPV may cause warts on or around the female and male genital organs and in the anal area. These warts may barely be visible or they may be several inches across. These are known as genital warts or condyloma acuminatum. Most cases of genital warts are caused by HPV 6 and HPV 11. They are called low-risk types of HPV because they are seldom linked to cancer. Other types of HPV are called high-risk types because they are strongly linked to cancers, including cancer of the cervix, vulva, and vagina in women, penile cancer in men, and cancers of the anus, mouth, and throat in both men and women. The high-risk types include HPV 16, HPV 18, HPV 31, HPV 33, and HPV 45, as well as some others. There might be no visible signs of infection with a high-risk HPV until pre-cancerous changes or cancer develops. Doctors believe that a woman must be infected with HPV in order to develop cervical cancer. Although this can mean infection with any of the high-risk types, about two-thirds of all cervical cancers are caused by HPV 16 and 18. Infection with HPV is common, and in most people the body can clear the infection by itself. Sometimes, however, the infection does not go away and becomes chronic. Chronic infection, especially when it is caused by certain high-risk HPV types, can eventually cause certain cancers, such as cervical cancer. The Pap test looks for changes in cervical cells caused by HPV infection. Other tests look for the infections themselves by finding

genes (DNA) from HPV in the cells. Some women are tested for HPV along with the Pap test as a part of screening. When a woman has a mildly abnormal Pap test result the HPV test may also be used to help decide what to do next. If the test results show a high-risk type of HPV, it can mean she will need to be fully evaluated with a colposcopy procedure. Although there is currently no cure for HPV infection, there are ways to treat the warts and abnormal cell growth that HPV causes.

2. Smoking

When someone smokes, they and those around them are exposed to many cancer-causing chemicals that affect organs other than the lungs. These harmful substances are absorbed through the lungs and carried in the bloodstream throughout the body. Women who smoke are about twice as likely as non-smokers to get cervical cancer. Tobacco by-products have been found in the cervical mucus of women who smoke. Researchers believe that these substances damage the DNA of cervix cells and may contribute to the development of cervical cancer. Smoking also makes the immune system less effective in fighting HPV infections.

3. Immunosuppression

Human immunodeficiency virus (HIV), the virus that causes AIDS, damages the immune system and puts women at higher risk for HPV infections. This might explain why women with AIDS have an increased risk for cervical cancer. The immune system is important in destroying cancer cells and slowing their growth and spread. In women with HIV, a cervical pre-cancer might develop into an invasive cancer faster than it normally would. Another group of women at risk of cervical cancer are women receiving drugs to suppress their immune response, such as those being treated for an autoimmune disease (in which the immune system sees the body's own tissues as foreign and attacks them, as it would a germ) or those who have had an organ transplant.

4. Chlamydia infection

Chlamydia is a relatively common kind of bacteria that can infect the reproductive system. It is spread by sexual contact. Some studies have seen a higher risk of cervical cancer in women whose blood test results show evidence of past or current chlamydia infection (compared with women who have normal test results). Women who are infected with chlamydia often have no symptoms.

5. Diet

Women whose diets don't include enough fruits and vegetables may be at increased risk for cervical cancer. Overweight women are more likely to develop adenocarcinoma of the cervix.

6. Oral contraceptives (birth control pills)

There is evidence that taking oral contraceptives (OCs) for a long time increases the risk of cancer of the cervix. Research suggests that the risk of cervical cancer goes up the longer a woman takes OCs, but the risk goes back down again after the OCs are stopped. In one study, the risk of cervical cancer was doubled in women who took birth control pills longer than 5 years, but the risk returned to normal 10 years after they were stopped. The American Cancer Society believes that a woman and her doctor should discuss whether the benefits of using OCs outweigh the potential risks. A woman with multiple sexual partners should use condoms to lower her risk of sexually transmitted illnesses no matter what other form of contraception she uses.

7. Intrauterine device use

A recent study found that women who had ever used an intrauterine device (IUD) had a lower risk of cervical cancer. The effect on risk was seen even in women who had an IUD for less than a year, and the protective effect remained after the IUDs were removed. Using an IUD might also lower the risk of endometrial (uterine) cancer. However, IUDs do have some risks. A woman interested in using an IUD should first discuss the potential risks and benefits with her doctor. Also, a woman with multiple sexual partners should use condoms to lower her risk of sexually transmitted illnesses no matter what other form of contraception she uses.

8. Multiple full-term pregnancies

Women who have had 3 or more full-term pregnancies have an increased risk of developing cervical cancer. No one really knows why this is true. One theory is that these women had to have had *unprotected intercourse to get pregnant*, so they may have had more exposure to HPV. Also, studies have pointed to hormonal changes during pregnancy as possibly making women more susceptible to HPV infection or cancer growth. Another thought is that pregnant women might have weaker immune systems, allowing for HPV infection and cancer growth. Young age at the first full-term pregnancy Women who were younger than 17 years when they had their first full-term pregnancy are almost 2 times more likely to get cervical cancer later in life than women who waited to get pregnant until they were 25 years or older.

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9. **Poverty**

Poverty is also a risk factor for cervical cancer. Many low-income women do not have ready access to adequate health care services, including Pap tests. This means they may not get screened or treated for cervical pre-cancers.

10. **Diethylstilbestrol (DES)**

DES is a hormonal drug that was given to some women to prevent miscarriage between 1940 and 1971. Women whose mothers took DES (when pregnant with them) develop **clear-cell adenocarcinoma** of the vagina or cervix more often than would normally be expected. This type of cancer is extremely rare in women who haven't been exposed to DES. There is about 1 case of this type of cancer in every 1,000 women whose mothers took DES during pregnancy. This means that about 99.9% of "DES daughters" do not develop these cancers.

Screening and down staging of cancer cervix

Cervical cancer screening is an essential part of a woman's routine health care. It is a way to detect abnormal cervical cells, including precancerous cervical lesions, as well as early cervical cancers. Both precancerous lesions and early cervical cancers can be treated very successfully. Routine cervical screening has been shown to greatly reduce both the number of new cervical cancers diagnosed each year and deaths from the disease.

Cervical cancer screening includes two types of screening tests: cytology-based screening, known as the Pap test or Pap smear, and HPV testing. The main purpose of screening with the Pap test is to detect abnormal cells that may develop into cancer if left untreated. The Pap test can also find noncancerous conditions, such as infections and inflammation. It can also find cancer cells. In regularly screened populations, the Pap test identifies most abnormal cells before they become cancer.

1. **Pap test**
2. **Liquid based cytology**
3. **Visual inspection**
4. **Visual inspection with acetic acid(VIA)**

5. **Visual inspection with lugol's Iodine(VILI)**
6. **Visual inspection with acetic acid with magnification(VIAM)**
7. **Cervical biopsy with histopathological examination**

1. Pap test-

A doctor may simply describe Pap test results to a patient as "normal" or "abnormal." It is important to remember that abnormalities rarely become cancerous, and even severe lesions do not always lead to cancer. Likewise, HPV test results can either be "positive," meaning that a patient is infected with at least one high-risk HPV type, or "negative," indicating that high-risk HPV types were not found. A woman may want to ask her doctor for specific information about her Pap and HPV test results and what these results mean.

Most laboratories in the United States use a standard set of terms, called the Bethesda System, to report Pap test results. Under the Bethesda System, samples that have no cell abnormalities are reported as "negative for intraepithelial lesion or malignancy." A negative Pap test report may also note certain benign (non-neoplastic) findings, such as common infections or inflammation. Pap test results also indicate whether the specimen was satisfactory or unsatisfactory for examination.

The Bethesda System considers abnormalities of squamous cells and glandular cells separately. Squamous cell abnormalities are divided into the following categories, ranging from the mildest to the most severe.

Atypical squamous cells (ASC) are the most common abnormal finding in Pap tests. The Bethesda System divides this category into two groups, which are described below.

- **ASC-US**: atypical squamous cells of undetermined significance. The squamous cells do not appear completely normal, but doctors are uncertain about what the cell changes mean. Sometimes the changes are related to an HPV infection, but they can also be caused by other factors. For women who have ASC-US, a sample of cells may be tested for the presence of high-risk HPV types. If high-risk HPV type is present, follow-up testing will usually be performed. On the other hand, a negative HPV test can provide reassurance that cancer or a precancerous condition is not present.
- **ASC-H**: atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion. The cells do not appear normal, but doctors are uncertain about what the cell changes mean. ASC-H lesions may be at higher risk of being precancerous compared with ASC-US lesions.

Low-grade squamous intraepithelial lesions (LSILs) are considered mild abnormalities caused by HPV infection. Low-grade means that there are early changes in the size and shape of cells.

Intraepithelial refers to the layer of cells that forms the surface of the cervix. LSILs are sometimes classified as mild dysplasia. LSILs may also be classified as cervical intraepithelial neoplasia (CIN-1).

High-grade squamous intraepithelial lesions (HSILs) are more severe abnormalities that have a higher likelihood of progressing to cancer if left untreated. High-grade means that there are more evident changes in the size and shape of the abnormal (precancerous) cells and that the cells look very different from normal cells. HSILs include lesions with moderate or severe dysplasia and carcinoma in situ (CIS). HSIL lesions are sometimes classified as CIN-2, CIN-3, or CIN-2/3. CIS is commonly included in the CIN-3 category.

Squamous cell carcinoma

Glandular cell abnormalities are divided into the following categories:

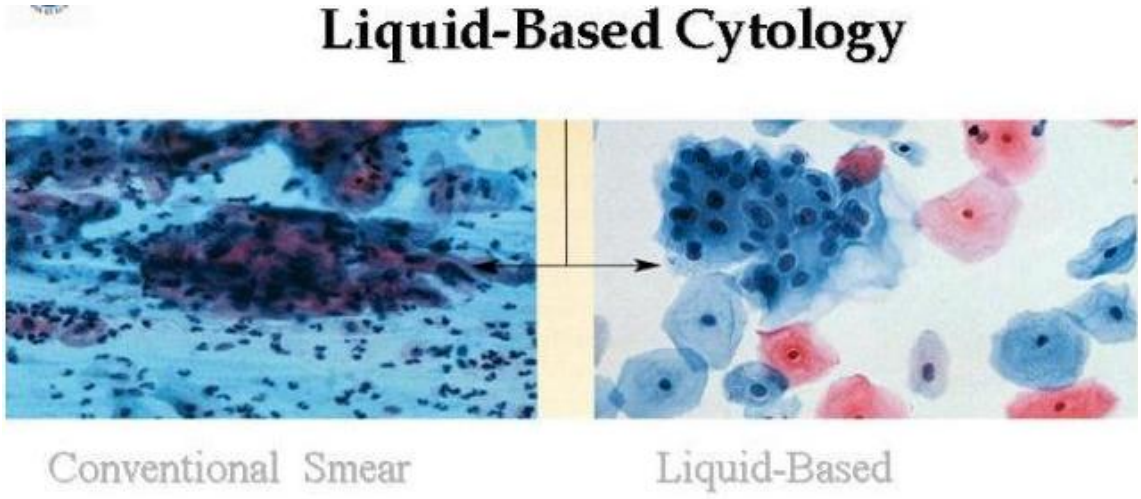
Atypical glandular cells (AGC).

Endocervical adenocarcinoma in situ (AIS)

Adenocarcinoma

2. Liquid based cytology-

Liquid-based Pap test technology requires placement of cervical samples into a vial of liquid preservative. During processing, non-diagnostic debris is partially removed and the number of white and red blood cells is markedly reduced. Fixed cells are then sedimented (SurePath) or filtered (ThinPrep) as a thin layer on a slide and stained. Thus, epithelial cells, diagnostically relevant cells, and infectious organisms are more clearly visible. Liquid-based technology results in a reduction in unsatisfactory slides relative to conventionally (non-liquid-based) prepared slides.



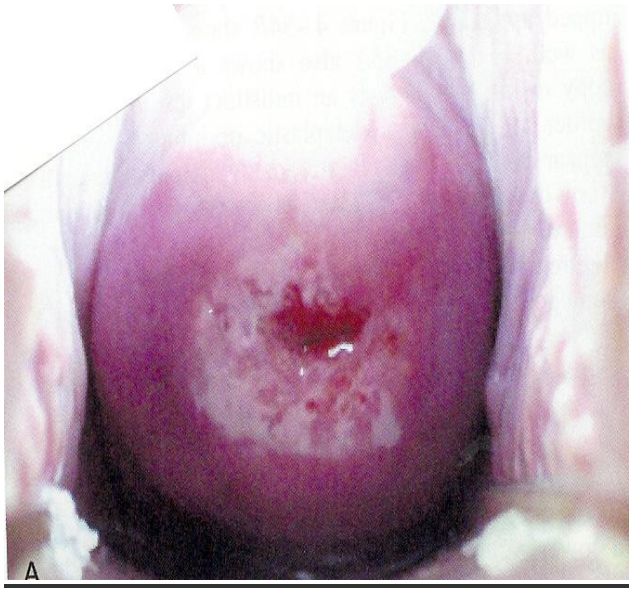
3. Visual inspection-

A simple per speculum examination can largely differentiate between the normal and abnormal cervix. Such patients can be screened further and the disease can be detected in early stages.

4. Visual inspection with acetic acid-

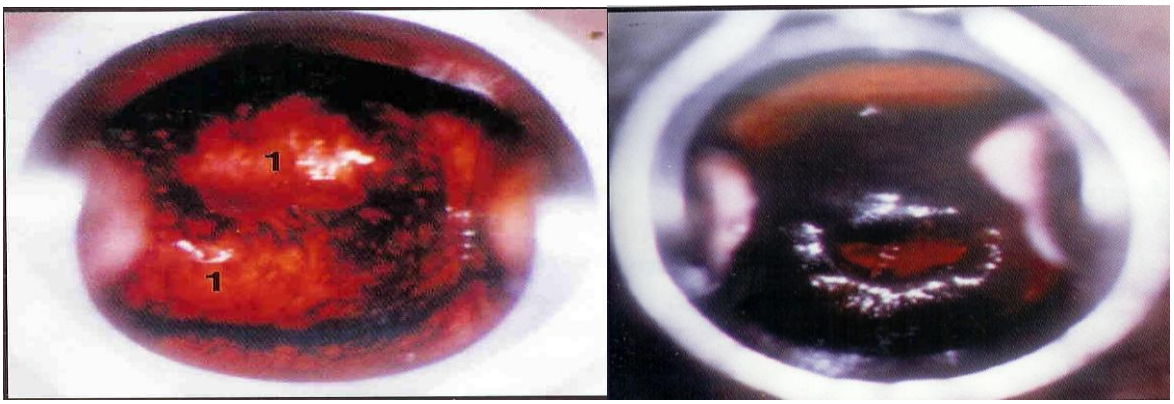
In visual inspection with acetic acid (VIA), 5% acetic acid is applied to the cervix with a large cotton swab and left for 30-60 seconds, after which the cervix is visually examined with the naked eye and a lamp. Pre-cancerous lesions, with a higher ratio of intracellular proteins, turn white when combined with acetic acid. Normal cervices without any precancerous lesions, do not change color. This is the same method used when physicians to colposcopy; using the change in color from acetic acid to guide biopsy.

VIA is an attractive alternative to PAP smears for its ease of use, low-cost and fewer physician visits. Currently, to do a PAP smear, the doctor requires a speculum, lamp, slide, cytobrush, microscope, pathologist and a 2-week or more follow-up visit. With VIA, any trained nurse or physician able to use a speculum can do the test. Tools needed include a speculum, lamp, cotton swab, and acetic acid (vinegar); there is no pathologist or physician needed. And, if the test is negative, the patient can be told immediately without having to return to the doctor for results. In rural areas where people travel hours for a doctors' visit, a screening method requiring fewer visits will have a much higher success rate.



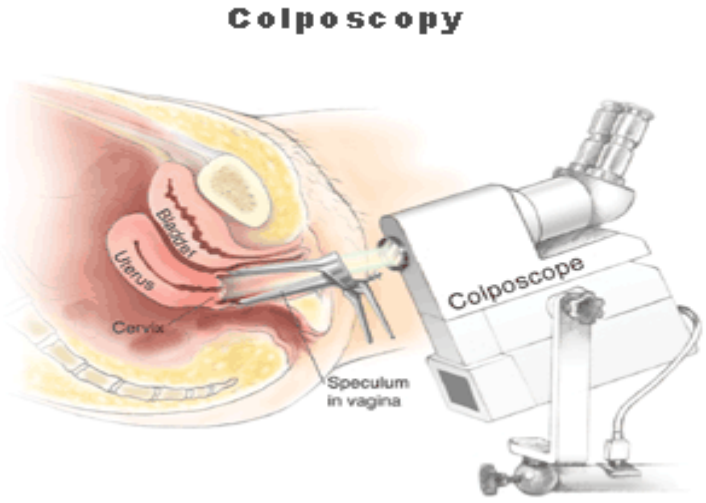
Visual inspection with Lugol's Iodine

Iodine uptake was noted as brown (positive uptake), yellow brown (partial uptake) and mustard yellow (no uptake). Areas of no uptake were considered as VILI positive while areas of partial uptake and positive uptake were considered as VILI negative. This was followed by colposcopy performed by the same observer in all cases after one hour or in the next visit.



Colposcopy

A colposcopy is a special way of looking at the cervix. It uses a light and a low-powered microscope to make the cervix appear much larger. This helps your health care provider find and then biopsy abnormal areas in your cervix.



Down-staging of cervical cancer

Down-staging is defined as a process of screening for cancer using clinical approaches for early detection of this disease. This is distinct from screening test and results in detection of the disease at a less advanced stage in the absence of screening. This experimental approach is applicable in developing countries where cytological screening is not possible in the near future. In this method paramedical staff trained for minimum period will be able to identify any abnormality including suspicious cervix and refer the case early to centres where facilities exist for treatment of premalignant and malignant lesions, including educating the women regarding risk factors, symptoms of the disease and prophylaxis. This experimental methodology recommended by WHO for developing countries like India has to be evaluated by monitoring various ongoing projects where visual inspection screening method is used. The results are collected which include feasibility, compliance, costing, referral methodology, difficulties in implementation, specificity, sensitivity, positive predictive value and drawbacks. The methodology of visual inspection and modified aided visual inspection, frequency and results of various studies in the Indian scenario is for recommendation of downstaging in MCH care. This is to be implemented in rural areas taking into consideration their cultural background and available infrastructure since cytology screening is not possible to cover even 20% of the existing cases in the near future

Referral

Any suspicious lesion detected by pap smear, visual methods, colposcopy are referred to higher center for targeted biopsy and planned management. So that the disease is detected in early stage and cancer related mortality and morbidity is detected in early stages.