Epidemiology, etio-pathogenesis and evaluation of gynaecological cancers

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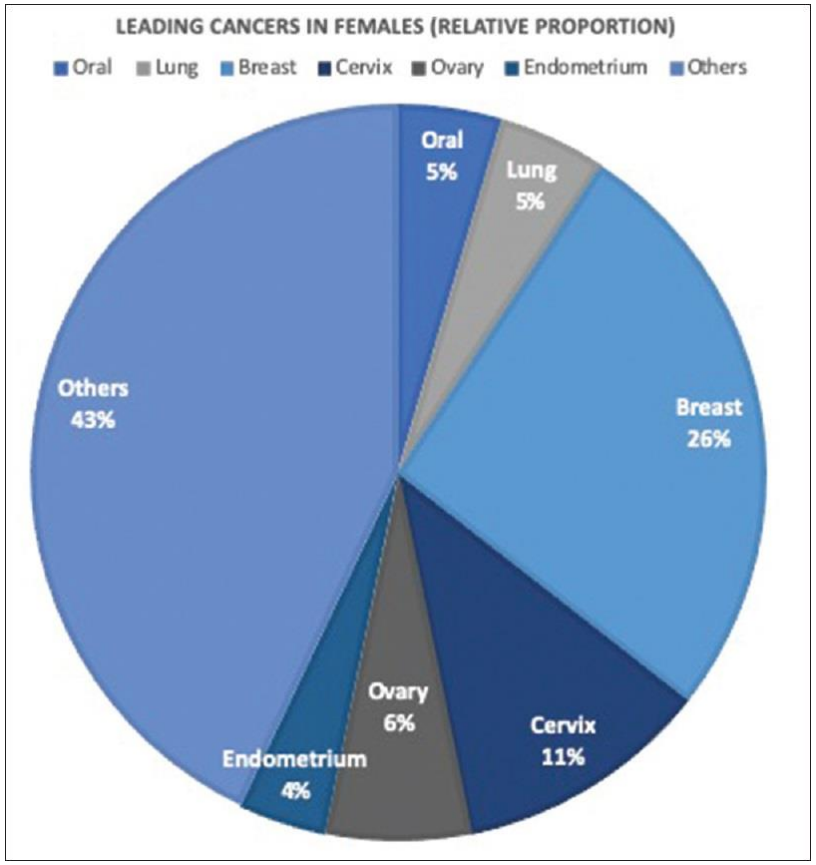
Specific learning objectives

- In the lecture, we shall learn about
- Present burden of Cervical, endometrial, ovarian and vulvar cancer in India
- Trends of gynecological cancer incidence and survival in India
- Etio-pathogenesis and risk factors of cervical cancer and implication in clinical practice
- Etio-pathogenesis of endometrial and ovarian cancers and implication in clinical practice
- Summary of standard evaluation of gynecological cancers

Cervical cancer

- GLOBOCAN 2020: 604,100 new cases globally in 2020 and 341,831 deaths
- In India, 123,907 new cervical cancer cases in 2020
- Second leading cause of cancer deaths for females in 12 Indian states

Cervical cancer



Cervical cancer : 11 % of female malignancies

In India

Trends in incidence cervical cancer - India

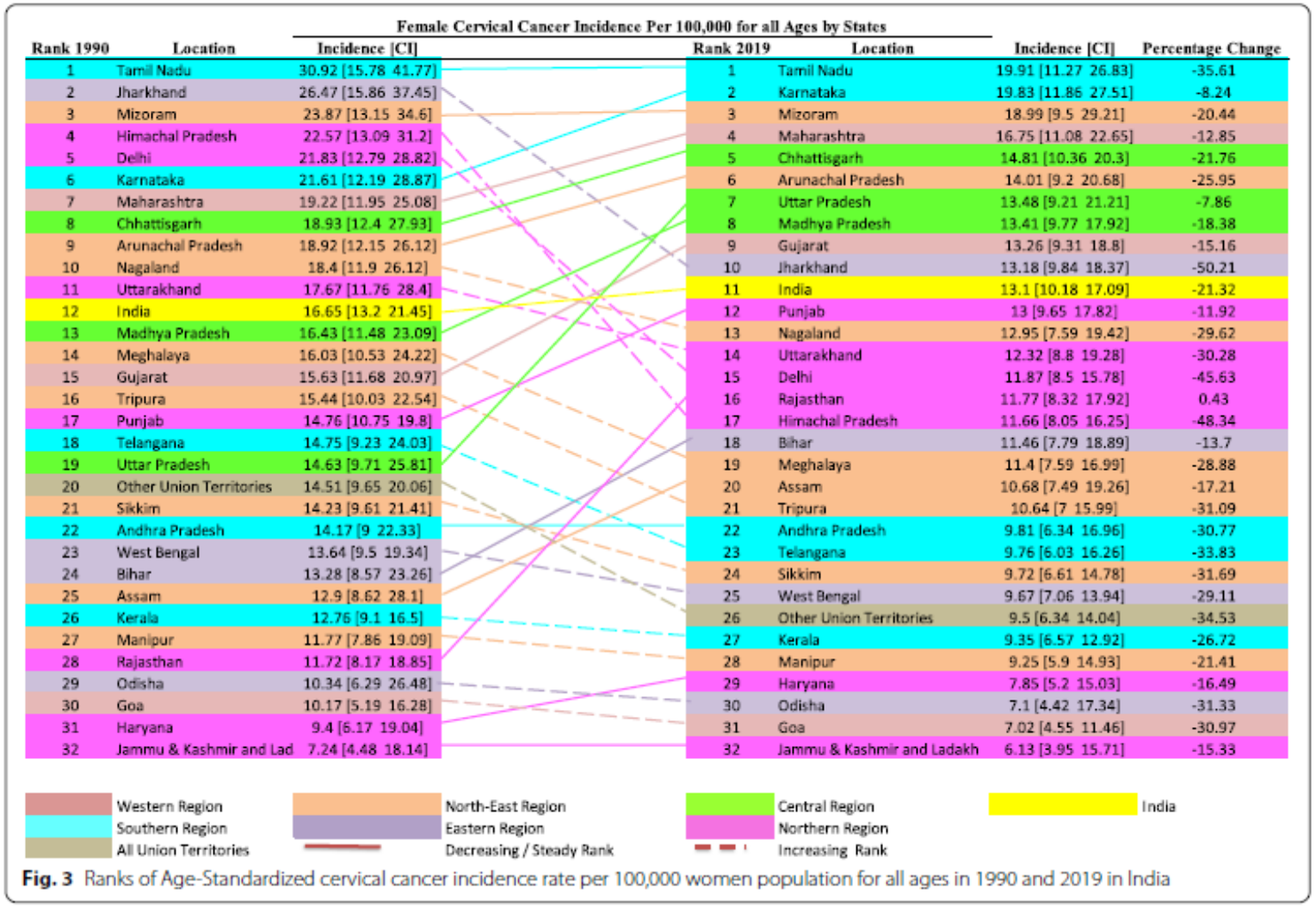


Fig. 3 Ranks of Age-Standardized cervical cancer incidence rate per 100,000 women population for all ages in 1990 and 2019 in India

Incidence per 100000
Decreased by 10 – 40%
(Most states) over 30 years

Trends in mortality cervical cancer - India

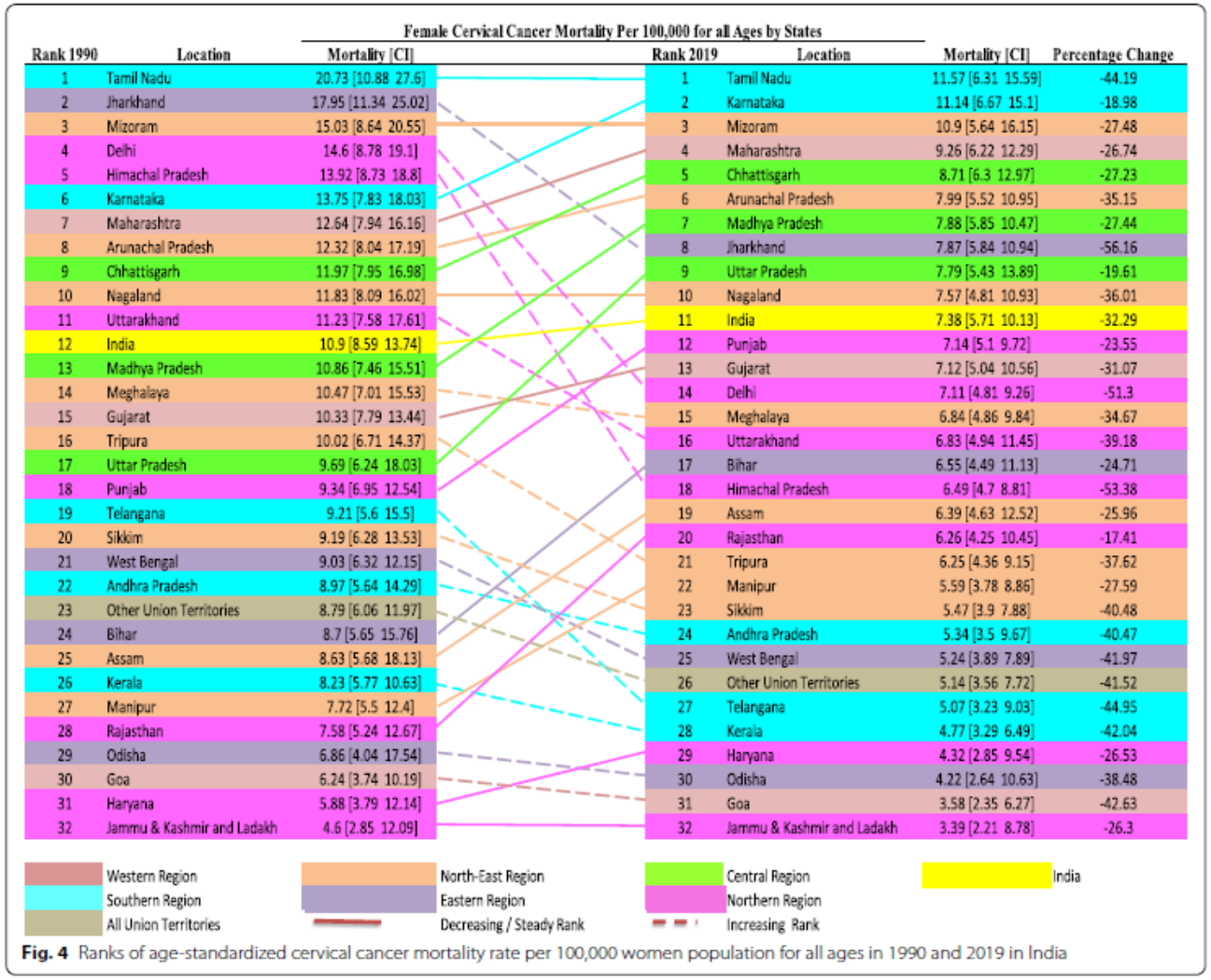


Fig. 4 Ranks of age-standardized cervical cancer mortality rate per 100,000 women population for all ages in 1990 and 2019 in India

Mortality per 100000
Decreased by 10 – 40%
(Most states) over 30 years

Trends in cervical cancer incidence India

- In high-income countries, cervical cancer incidence and mortality (per 100000) have decreased by more than 50% over the past 30 years
- India, incidence and mortality has come down by 10 – 40%
- The rising age at marriage, increase in the age at first term pregnancy, lowering parity could have contributed to reducing the risk of HPV acquisition, decreasing the incidence of cervical cancer in India

Risk factors of cervical cancer	
HPV	Cigarette smoking
Immunosuppression	Long-term use of intra-uterine device
Chlamydia infection	Multiple full-term pregnancies
Number of sexual partners	Giving birth younger than 17 years
Sexual activity from an early age	Poverty
Family history	Long-term use of oral contraceptives

Etio-pathogenesis cervical cancer - HPV

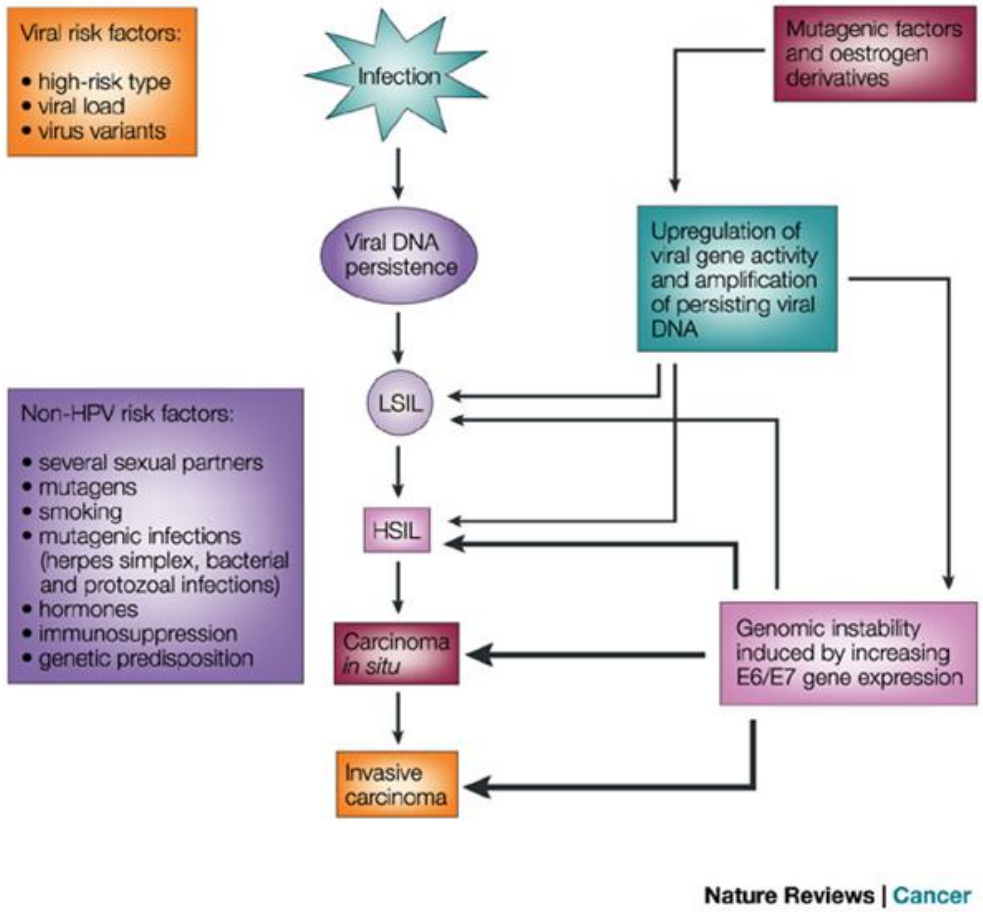
- There are more than 130 types of known HPV with 23 HPV types identified as cancer-related

Table 1. Classification of α-type human papillomavirus (α-HPV) genotypes by carcinogenic potential

Group 1	Carcinogenic to humans	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 68, 59
Group 2A	Probably carcinogenic to humans	HPV 68
Group 2B	Possibly carcinogenic to humans	HPV 26, 53, 64, 65, 66, 67, 69, 70, 73, 82
Group 3	Not classifiable as to carcinogenicity in humans	HPV 6, 11

- HPV 16 and 18 are the most commonly found HPV in invasive cervical cancer

Etio-pathogenesis cervical cancer - HPV



Etio-pathogenesis cervical cancer - HPV

- There are two main outcomes from the integration of HPV viral DNA into the host genome that can eventually lead to tumour formation.

1. Blocking the cell apoptotic pathway

2. Blocking synthesis regulatory proteins leading to uncontrolled mitosis

- Two integral genes in the HPV genome play a central role in tumour formation

1. E6 - inhibits the role of p53
2. E7 - inhibits the role of the retinoblastoma protein (Rb)

In normal physiology, p53 and Rb are involved in the regulation of cells with damaged/mutated DNA.

Pathogenesis of cervical cancer – From CIN to SCC

- Invasive squamous cell carcinoma of the cervix, which is the commonest histological type, is preceded by a pre-invasive stage of the disease – CIN

- A large retrospective follow-up study of mild, moderate and severe dysplasia by Holowaty et al. showed that the majority of cases of mild (62.2%) and moderate dysplasia (53.7%) regressed (two negative smears within 2 years) while progression to moderate dysplasia or worse was approximately 25% within 5 years

What can be done to reduce cervical cancer mortality

- WHO recommendations for cervical cancer elimination
- Three key steps: vaccination, screening and treatment.
- Targets to reach by 2030
- 90% of girls fully vaccinated with the HPV vaccine by 15 years of age
- 70% of women screened using a high-performance test by age 35 and again by 45
- 90% of women identified with cervical disease receive treatment (90% of women with pre-cancer treated and 90% of women with invasive cancer managed).

HPV Vaccine

Do vaccines significantly reduce cervical cancer mortality?

What is the scenario in Indian context?

HPV Vaccine efficacy

- Population based cohort study of 1,672,983 women published in NEJM in 2020

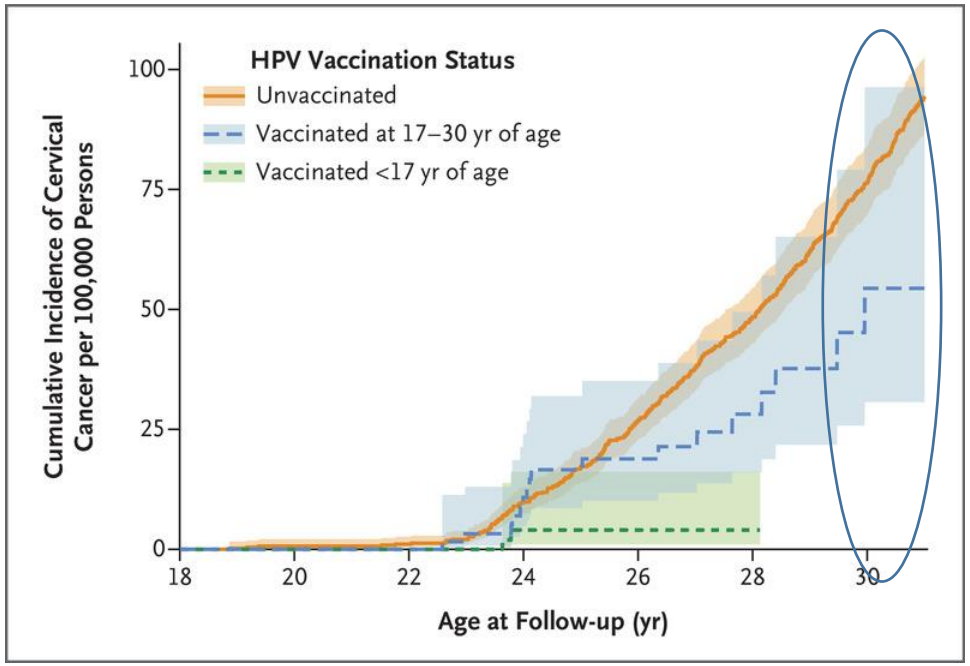


Table 2. HPV Vaccination and Invasive Cervical Cancer.

HPV Vaccination Status	No. of Cases of Cervical Cancer	Crude Incidence Rate per 100,000 Person-Yr (95% CI)	Age-Adjusted Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)*
Unvaccinated	538	5.27 (4.84–5.73)	Reference	Reference
Vaccinated	19	0.73 (0.47–1.14)	0.51 (0.32–0.82)	0.37 (0.21–0.57)
Status according to age cutoff of 17 yr				
Vaccinated before age 17 yr	2	0.10 (0.02–0.39)	0.19 (0.05–0.75)	0.12 (0.00–0.34)
Vaccinated at age 17–30 yr	17	3.02 (1.88–4.86)	0.64 (0.39–1.04)	0.47 (0.27–0.75)
Status according to age cutoff of 20 yr				
Vaccinated before age 20 yr	12	0.49 (0.28–5.73)	0.52 (0.29–0.94)	0.36 (0.18–0.61)
Vaccinated at age 20–30 yr	7	5.16 (2.46–10.83)	0.50 (0.24–1.06)	0.38 (0.12–0.72)

* The adjusted incidence rate ratios were adjusted for age as a spline term with 3 degrees of freedom, county of residence, calendar year, mother's country of birth, highest parental education level, highest annual household income level, previous diagnosis in mother of CIN3+, and previous diagnosis in mother of cancers other than cervical cancer. The 95% confidence intervals were bias-corrected percentile confidence intervals that were estimated with the use of bootstrapping with a resampling frequency of 2000 times.

HPV vaccine in India

- Although the HPV vaccination was introduced in India in 2008, it is yet to be included in the universal immunization program in India
- A vaccine delivery and demonstration project led by an international non-profit organization, PATH, was started in 2009 in Andhra Pradesh and Gujarat but had to be suspended in 2010 as a result of public concern, allegedly arising from the deaths of seven girls who received HPV vaccine
- In 2016, an expert group ICMR reviewed available data on safety and efficacy and recommended HPV vaccines in girls 9 – 13 years (2 doses)

HPV vaccine in India

- Once the recommendations were received, a first of its kind HPV vaccination program for school children was launched in New Delhi
- Simultaneously, the Government of Punjab initiated a similar campaign and succeeded in vaccinating young girls with 97.5% and 98.5% coverage initially
- The Government of Sikkim also introduced HPV vaccination along similar lines and achieved high coverage and safety in 2018

Cervical cancer screening programme in India

- Existing health care providers (HCPs) at various facilities were supposed to roll out the population-based cancer screening in the country but lacked resources or expertise to do so
- To support the implementation of the cervical cancer screening program, the ICMR-NICPR was designated as a training hub for the Project ECHO (Extension for Community Healthcare Outcomes) model for training health care providers in cancer screening
- A study was conducted which reported the effectiveness of the training program in reaching primary care physicians/other HCPs across the country and improving their knowledge and skills related to screening for breast, oral, and cervical cancer.

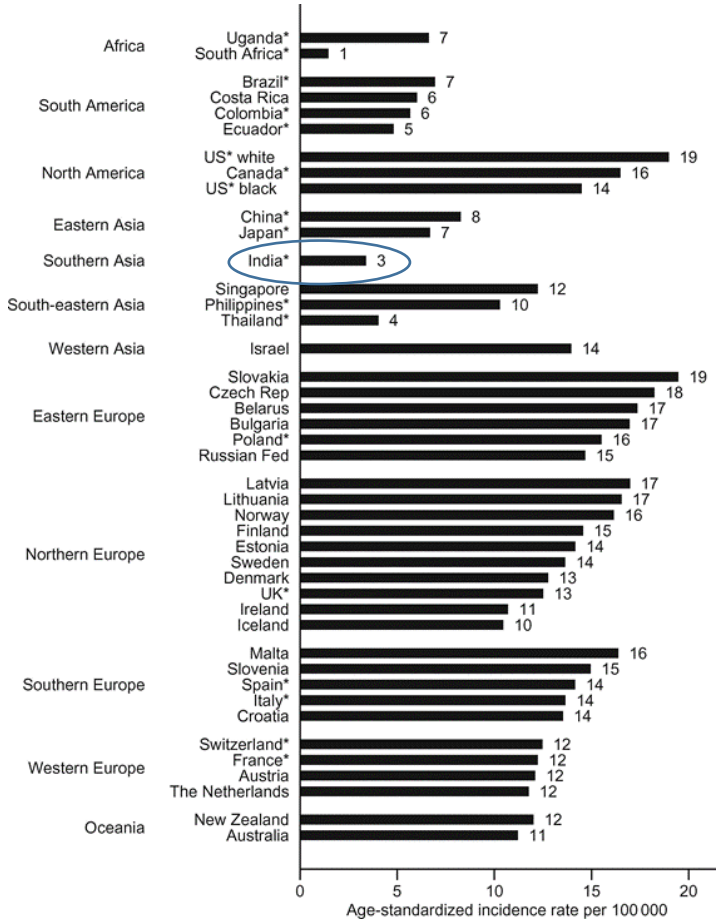
Cervical cancer screening programme in India

- The preparedness of the Indian healthcare system for implementing large-scale cervical cancer screening is a concern
- Dhillon et al. reported in their study that overall, readiness scores were low for cervical cancer screening.
- At Sub Health Centres, the lowest scores were observed in infrastructure (0.55) and infection prevention (0.44) while Primary Health Centres (PHCs) had low potential staffing scores (0.50) due to limited manpower

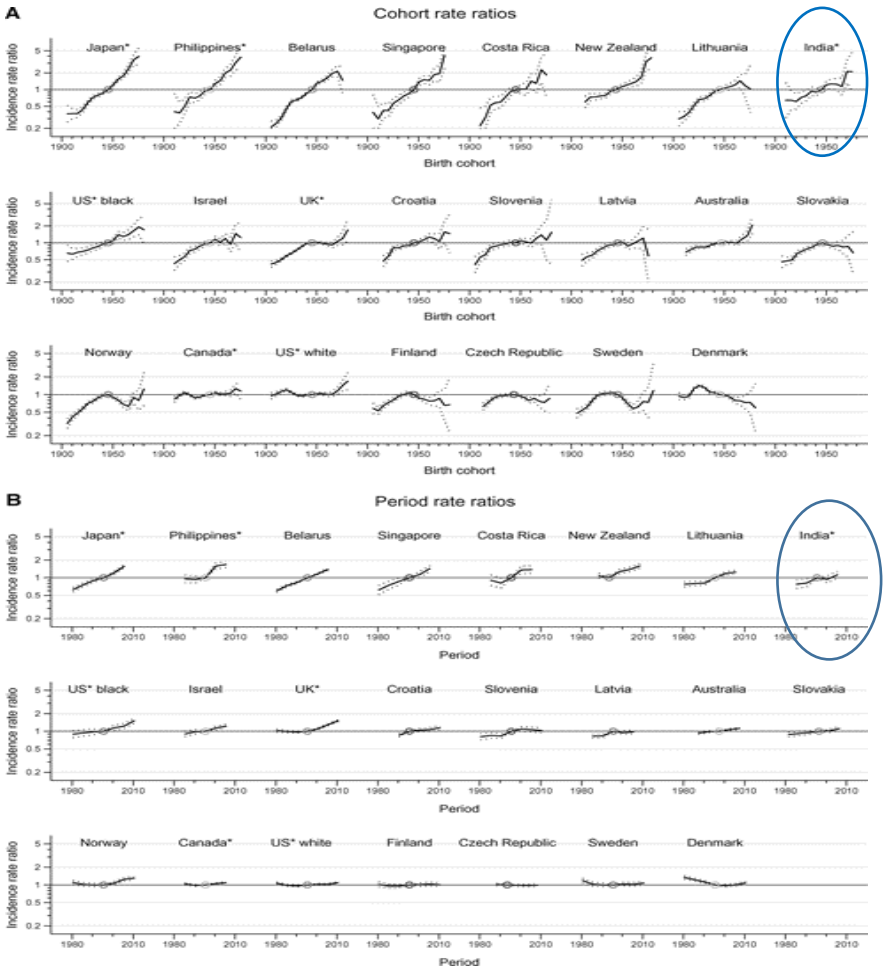
Endometrial cancer

- Carcinoma endometrium is the most common gynecological cancer in developed countries with an age standardized incidence rate (world) of 8.4 per 100,000 women
- The age standardized incidence rate (ASIR) of endometrial cancer in India is 2.3/100,000 women
- In India, the total number of estimated new cases of endometrial cancer in 2018 is 13,328 with an estimated 5010 deaths
- The peak ages of diagnosis are between ages 55 and 64 years (median 62 years).
- The rise in endometrial cancer in India is mainly attributed to changing trends in the lifestyle and reproductive profile of women, especially in urban areas

Endometrial cancer – India vs other countries



Trends in incidence of endometrial cancer

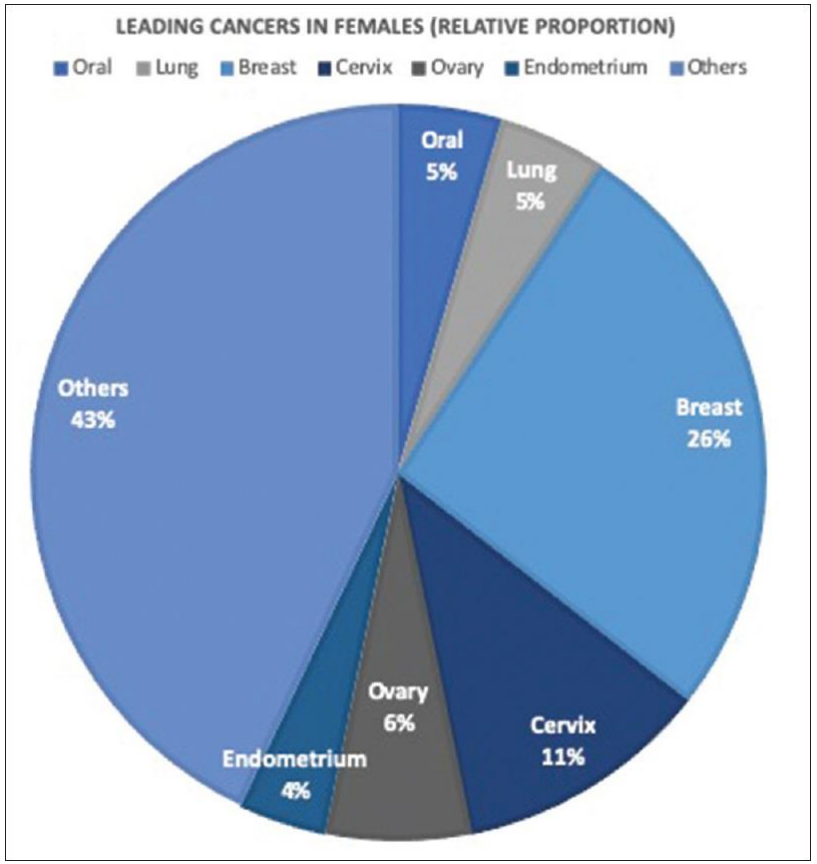


Increasing incidence across world

Figure based on birth cohort (i.e. year of birth)

Time period in figure 1900 to 2010

Endometrial cancer



Endometrial cancer: 4% of female malignancies in India

Risk factors for endometrial cancer India

- Estrogen only hormonal therapy
- Early menarche
- Late menopause
- Nullipartity
- PCOS
- Age > 55 years
- Family history of Lynch syndrome
- Obesity
- Previous pelvic RT
- Tamoxifen use

Etiology of endometrial cancer

- Endometrial cancers are divided into Type 1 (Endometrioid) and Type 2 (Serous and clear cell) endometrial cancers
- Pathogenesis of most endometrial endometrioid carcinoma begins with uninterrupted endometrial proliferation, hormonally stimulated by endogenous or exogenous estrogen unopposed by progesterone
- The above leads to endometrial hyperplasia
- PTEN, k RAS mutations, microsatellite instability and near diploid karyotype then add on to development of carcinoma

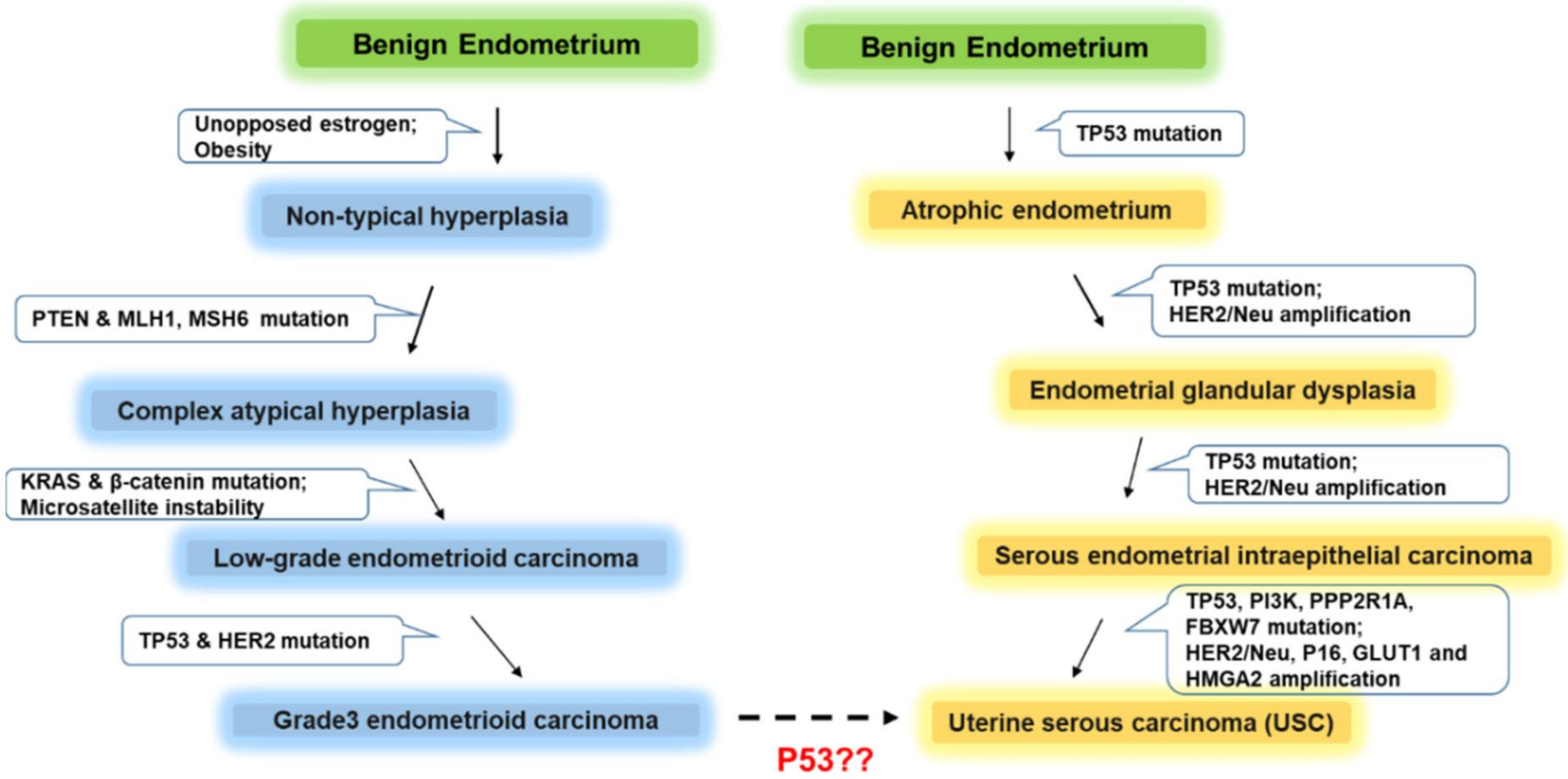
Pathogenesis of endometrial cancer – Type 1

- Type I endometrial cancers display a wide range of genetic alterations which differ in their temporal sequence
- Most common genetic alteration in Type I endometrial cancer is *PTEN* inactivation (Upto 83%)
- Mutations in *KRAS* causing aberrant activation have been implicated in 10-30% of Type I endometrial cancers
- Gain of function mutations in exon 3 of the *CTNNB1* gene (β-catenin) are also observed in 25-38% of Type I cancers
- Aberrant accumulation of inactive p53 protein is observed in only 5% of Type I endometrial cancers

Pathogenesis of endometrial cancer – Type 2

- The primary genetic defect is mutation of the p53 gene, observed in 75-100% of tumors
- Amplification or overexpression of HER2 has also been reported in 20% of Type II endometrial cancers
- In contrast with Type I tumors, inactivation of PTEN and RAS is not observed
- Papillary serous and clear cell carcinoma have low expression of estrogen and progesterone receptors

Pathogenesis pathway – Endometrial cancer



5 year overall survival in endometrial cancer

- Stage IA 90.8%
- Stage IB 86.1%
- Stage IIB 79.2%
- Stage IIIA 66.2%
- Stage IIIB 49.9%
- Stage IIIC 57%
- Stage IVA 25.5%
- Stage IVB 20%

Ovarian cancer

- In 2020, 21,750 new ovarian cancer comprised 1.2% of all cancer cases in the world
- Estimated number of deaths 13,940
- The 5-year relative survival rate is expected to be 48.6%
- Around 15.7% of the ovarian cancer cases are diagnosed at the localised stage (5 year OS: 93%), about 58% at stage IV (5 year OS: 30%)

Ovarian cancer - India

- The estimated age-adjusted incidence varies from 0.9 – 8.4 per 100,000 women in various population based cancer registries in India
- The incidence of ovarian cancer increases with age.
- The age specific incidence rate (ASIR) increases from age 35 years and peaks between the ages of 55-64 years.
- Most population-based cancer registries have documented a gradual increase in the incidence of ovarian cancer over the years.

Risk factors – Ovarian cancer

- Oestrogen hormone replacement therapy (HRT), tobacco smoking and exposure to asbestos.
- There is limited evidence regarding perineal use of talc-based body powder and exposure to X-radiation and gamma radiation
- A long oestrogen window (early menarche and late menopause) also correlates strongly with risk of ovarian cancer
- Nulliparity and older age at first childbirth (more than 35 years) confers an increased risk of developing ovarian cancer

Risk factors – Ovarian cancer

- There is a strong genetic predisposition for ovarian cancer
- A family history of ovarian cancer in 2 or more first-degree relatives increases risk and is also associated with an early onset disease
- A personal history of breast cancer prior to 40 years of age, or a personal history of breast cancer prior to 50 years of age with a family history of breast or ovarian cancer also increase the risk
- Women of Eastern European (Ashkenazi) Jew descent are a special category at high risk

Risk factors – Ovarian cancer

- Studies on other potential risk factors, such as obesity, infertility, endometriosis, sedentary lifestyle, smoking and alcohol consumption have conflicting results
- Recent data suggests that pelvic inflammatory disease may increase the risk of ovarian cancer

Etio-pathogenesis of ovarian cancers

- Ovarian cancers are heterogenous
- The major types of malignant epithelial ovarian tumors are- serous adenocarcinoma, mucinous adenocarcinoma, endometrioid adenocarcinoma, clear cell carcinoma, transitional carcinoma, squamous carcinoma, undifferentiated carcinoma and mixed carcinoma
- It is recently proposed that there are two distinct types of ovarian serous carcinomas- low grade (type I) and high grade (type II).

Etio-pathogenesis of ovarian cancers

- Type 1 and type 2 represent two different entities with differing pathogenesis, molecular events, natural history, biological behavior, response to therapy and prognosis
- Low grade indolent, slow growing and shows poor response to platinum based therapy. Although it usually results in death of the patient, it is compatible with prolonged survival.
- High grade OSC are aggressive, show initial response to platinum based therapy but shows recurrence and are eventually fatal

Molecular differences – Type 1 and Type 2

Type 1 ovarian cancer	Type 2 ovarian cancer
K RAS or BRAF mutations	No K RAS or BRAF mutations
Lower expression of mib1, BCL2, p16, ki67, c-kit	Higher expression
Express WT1	Express WT1
ER, PR present	No ER, PR

Vulvar cancer

- Vulvar cancer accounts for 0.2% of new cases and 0.2% of new deaths of all sites worldwide making it an uncommon malignancy according to Global Cancer Statistics 2020
- In the Indian case scenario, carcinoma of vulva ranks 33 in number accounting for 0.26% of new cases and 0.02% of deaths from all sites

Summary of Published Indian Data

Author With the Type of Study	No of Cases	Stages Wise Distribution	The Period of Study	HPE	Treatment Modality (No of Patients)	Follow-Up	Survival Analysis
North India							
Singh et al[12] Retrospective cohort study Indian Journal of Cancer 2021	41	Stage Ia: 1 Stage Ib and II: 19 Stage III: 16 Stage IV: 5	2004-2014 10 years	SCC	Wide local excision: 1 Simple vulvectomy: 12 MRV: 7 Definite RT: 11 CT: 3 CTRT: 7	—	Stage I + II: 76.9% with a mean survival of 5 years Stage III + IV: 30% with a mean survival of 12 months
Sharma et al[13] Retrospective study Indian Journal of Cancer and Therapeutics 2021	60	Stage I: 2 Stage II: 17 Stage III: 31 Stage IV: 9 Unknown: 1	1998-2005 8 years	SCC	Surgery: 33 PAL RT: 12 Definite RT: 15	23 months	41% all stage Stage I: 100% Stage II: 60% Stage III: 41% Stage IV: 0%
Modi et al[20] Retrospective study Journal of Gynecological Surgeries 2016	78	Stage I: 55 Stage II: 20 Stage III: 3	2007-2014 8 years	SCC	Radical local excision: 4 MRV: 10 Radical vulvectomy: 64 Reconstruction: 12	33 months	2-year DFS: 100% with no nodal involvement 73.5% with U/L nodal involvement, 60% with B/L nodal involvement
Mazumder et al[24] Retrospective study The South Asian Journal of Cancer 2020	50	66% of patients in stage III + IV	2008-2014 7 years	SCC	WLE: 2 Radical vulvectomy: 20 MRV: 14 14 did not undergo surgery Adjuvant RT including PAL: RT: 40	25.5 months	OS: 31 months DFS: 25 months
Singhal et al[19] Retrospective study Journal of Cancer Research and Therapeutics 2021	30	Stage I + II: 19 Stage III + IV: 10 Incompletely staged: 1	2010-2016 7 years	SCC	Simple vulvectomy: 3 Radical vulvectomy: 24 WLE: 3	—	Stage I + II: 49% Stage III + IV: 24.8%
Kumar et al[17] Retrospective study Journal of Cancer Research & Therapeutics 2017	16	NA	2011-2015 5 years	SCC	Surgery	24 months	Stage I: 24 months Stage II: 31 months Stage III: 18 months
Kumar et al[11] Retrospective review Journal of Egyptian National Cancer Institute 2020	20	Stage I: 6 Stage II: 1 Stage III: 11 Stage IV: 2	2014-2019 5 years	SCC	WLE: 15 Radical vulvectomy: 4 MRV: 1 NACT: 1 Adjuvant RT: 18	11.1 months	66%: 5-year DFS
Lakhwani et al[25] Case series Indian Journal of Surgical Oncology 2019	5	Stage I: 5	2016-2018 2 years	SCC	MRV: 3 Modified radical anterior hemi vulvectomy: 2	6 months: 2 year	No mortality was reported
South India							
Bafna et al[14] Retrospective review Journal of Obstet and Gynecol 2004	37	Stage I: 3 Stage II: 7 Stage III: 16 Stage IV: 11	1996-2000 5 years	SCC	WLE: 1 Radical vulvectomy: 6 Radical vulvectomy with B/L GND: 25 Neoadjuvant RT: 1 PAL CT: 4	8 months: 2 years	—
Jeevarajan et al[16] Retrospective study Indian Journal of Surgical Oncology 2017	39	Stage I: 20 Stage II: 4 Stage III: 13 Stage IV: 02	2004-2013 10 years	SCC	Radical vulvectomy: 28 Simple vulvectomy: 4 Hemi vulvectomy: 2 WLE: 5	32 months	OS: 85.1% DFS: 65.4% 87.5%: node negative 70%: node positive
Singareddy et al[23] Retrospective study Journal of Cancer Research & Therapeutics 2019	76	Stage I: 43 Stage II: 21 Stage III: 11 Stage IV: 01	2007-2016 10 years	SCC	Surgery: 59 RT: 17	35 months	DFS at 3 years was 45.3% in surgery and 35.5% in the RT group
East India							
Deka et al[10] Retrospective study Journal of Midlife Health 2014	18	Stage I: 2 Stage II: 6 Stage III: 6 Stage IV: 4	2006-2009 3 years	SCC	Surgery: 18 Adjuvant RT: 10	—	—
Nandwani et al[9] Retrospective study Journal of Obstet and Gynecol 2019	29	Stage I: 5 Stage II: 8 Stage III: 13 Stage IV: 03	2017-2018 2 years	SCC	Simple vulvectomy: 1 WLE: 5 MRV: 9 PAL RT: 2 CCTRT: 10 PORT: 12	—	—
West India							
Chhabra et al[3] Retrospective study Journal of Obstet and Gynecol 2015	18	Stage I: 4 Stage II: 1 Stage III: 3 Stage IV: 4 Stage VIN: 6	1984-2004	—	Surgery: 11	—	Decreasing trends of vulvar cancer 2.25% between 1984 and 1988, to 0.33% between 2004 and 2008
Poddar et al[22] Retrospective study Obstetrics and Gynecological Sciences 2020	111	Stage I: 58 Stage II: 11 Stage III: 42	2005-2015 10 years	SCC	Surgery: WRE or radical vulvectomy	22.8	Mean OS: 27.8 months Mean DFS: 26 months
Rajshree et al[26] Retrospective cohort study International Journal of Cancer Therapy and Oncology 2018	20	Stage I: 1 Stage II: 5 Stage III: 7 Stage IV: 7	2013-2017 4.5 years	SCC	WLE: 3 Radical vulvectomy: 5 RT: 7 CTRT: 9	23 months	OS: 51%

Abbreviations: B/L, bilateral; CCTRT, concurrent chemoradiotherapy; CT, chemotherapy; DFS, disease free survival; GND, groin node dissection; HPE, histopathology examination; MRV, modified radical vulvectomy; NACT, neoadjuvant chemotherapy; OS, overall survival; PAL RT, palliative radiotherapy; PORT, postoperative radiotherapy; RT, radiotherapy; SCC, squamous cell carcinoma; U/L, unilateral; WLE, wide local excision; WRE, wide radical excision.

Epidemiology of vulvar cancer

A study from Maharashtra showed a decreasing trend of vulvar cancer over 24 years from 2.25% to 0.03%

Two different studies performed from tertiary oncology institute in northeastern state by Nandwani et al and Deka et al showed a rise in trend over the period

The mean age of presentation 60 years

Commonest histology squamous cell carcinoma

More than 50% of the patients presented in the locally advanced stage of the disease

Risk factors – Vulvar cancer

- Increasing age
- Infection with human papillomavirus (HPV)
- Smoking
- Inflammatory conditions of the vulva
- Prior pelvic radiation
- Immunodeficiency

Evaluation of cervical cancer

- Clinical evaluation by examination and if needed colposcopy
- Histological diagnosis with biopsy
- MRI pelvis
- CECT TA
- Cystoscopy, sigmoidoscopy if doubtful finding of infiltration on examination or imaging
- CBC/ LFT/ KFT

Evaluation of endometrial cancer

- Transvaginal sonography
- Endometrial and endo-cervical sampling
- Hysteroscopy: Evaluation with hysteroscopy advised for women with negative or inadequate sampling and strong suspicion of malignancy
- Magnetic Resonance Imaging (**MRI**): In case hysteroscopy findings are inconclusive, MRI to rule out any abnormality
- CT scan utilized for assessing extra-pelvic disease and lymph node involvement
- PET CT not indicated
- Serum CA 125 and Serum HE4 may be elevated

Evaluation of ovarian cancer

- CBC/ LFT/ KFT
- Serum tumor markers: CA-125, CEA, CA 19.9
- Imaging studies. Ultrasonography of abdomen and pelvis (transabdominal and transvaginal) is the usual first investigation for assessment of an undiagnosed adnexal mass and/or ascites or of symptom complex suggestive of ovarian mass
- Accuracy of good quality ultrasonography with colour Doppler, CT scan and MRI are similar (sensitivity about 90% and specificity 85%) for differentiating benign from malignant ovarian masses
- X-ray chest or CT scan of the chest

Evaluation of ovarian cancer

- Ascitic fluid/ pleural fluid cytology (if ascitic or pleural fluid present)
- Fine needle aspiration cytology (FNAC)/ biopsy of the mass should be done only if primary surgery is not indicated, prior to starting neoadjuvant chemotherapy
- RMI score = Ultrasound score x menopausal score x CA125 level

Evaluation of vulva cancer

- The gold-standard for diagnosing vulvar cancer remains **histologic diagnosis**
- Any suspicious lesion including inguinal nodes should be **biopsied**
- Imaging studies indicated to evaluate the extent of the disease
- **MRI pelvis** preferred for local staging
- **CECT-TA** for FIGO stage III - IVA
- If there is suspicion of bladder or rectal involvement, cystoscopy and proctoscopy should be performed
- In Paget’s disease, screening should be done for other malignancies, including genitourinary, gastrointestinal, and breast cancer

Thank you