

HPV related disease in female and male

- Papillomaviruses are double-stranded deoxyribonucleic acid (DNA) viruses

HPV infection is the most common sexually transmitted infection worldwide. It can be contracted by **sexually active** individuals, both men and women, and it is more prone in women, with an estimate suggesting that **80%** of women could acquire genital HPV by the age of 50.

Ninety percent of HPV infections **resolve** within 2 years on average.

The International Agency for Research on Cancer (IARC) now recognizes **229 HPV genotypes**, with the list growing

- **High-Risk (Oncogenic) HPV Types** : Associated strongly with cervical, anal, oropharyngeal, vulvar, vaginal, and penile cancers. Most important **high-risk types**: HPV **16** –highest cancer risk
HPV **18** – second highest Others: **31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68**
- **Probably High-Risk / Intermediate-Risk Types**: These have some evidence of oncogenic potential but lower than the group above. HPV **26, 53, 67**
- **Low-Risk (Non-oncogenic) HPV Types**: Cause genital warts and low-grade lesions, but rarely lead to cancer. Major low-risk types: HPV **6** HPV **11** Additional low-risk types: **40, 42, 43, 44, 54, 61, 72, 81, 89**
- **Cutaneous (Skin) HPV Types**: Primarily cause common skin warts (non- genital).
Examples: HPV **1, 2, 3, 4, 7, 10, 27, 57**

Cutaneous warts

- Common and plantar warts: 1, 2, and 4
Flat warts: 3,10
Butchers wart: 7, 2



- occur most commonly in children and young adults
- more common among certain occupations, such as handlers of meat, poultry, and fish
- spread from skin surface to skin surface
- **10 percent** of children
- peak incidence: 12 and 16 years old
3.5 percent of adults

Other cutaneous diseases

- Bowen's disease
- Genital: 16
- Extragenital: 2, 3, 4, 16



Other cutaneous diseases

- Epidermodysplasia
verruciformis: 2, 3, 5, 8, 9,
10, 12, 14, 15, 17



چه بیماریهایی را در غشاهای مخاطی ایجاد می کند؟

- HPV می تواند در مخاط آنورثیتال، مخاط دهان و حلق و حتی در مخاط حنجره و اپی تلیوم تنفسی ایجاد ضایعات پاپیلومایی، کند.

بیماریهایی که در مخاط آنوز نیتال ایجاد می
کند:

Genital warts(Condyloma acuminatum)

- Prevalence: 1 to 10 percent
- The peak prevalence occurs between the ages of **17 and 33** years
- peak incidence in **20 to 24 years**
- HPV types **6 and 11**: 90% of genital warts
- External CA typically manifest as soft **papules or plaques**

Genital warts(Condyloma acuminatum)

- External anogenital warts are typically found on the vulva, penis, groin, perineum, anal skin, perianal skin, and/or suprapubic skin
- The CA can be single or multiple, flat, dome-shaped, cauliflower-shaped, filiform, fungating, pedunculated, cerebriform, plaque-like, smooth (especially on the penile shaft), verrucous, or lobulated

Genital warts (Condyloma acuminatum)

- warts may be white, skin-colored, erythematous (pink or red), violaceous, brown, or hyperpigmented. Anogenital warts are usually soft to palpation and can range from **1 mm to more than several centimeters** in diameter. The warts are typically asymptomatic but can occasionally be pruritic.



Genital warts(Condyloma acuminatum)

- HPV infection can enter a latent phase without signs or symptoms
- In patients who develop CA, the usual incubation period is 3 weeks to 8 months
- The cumulative incidence of genital wart development over 24 months was 58 to 64 percent

Wart on Perineal or Anal Area of a Child

- HPV types detected in lesions from children are more variable
- HPV types associated with cutaneous warts (eg, HPV 1 to 4 and others) are frequently detected in anogenital lesions from children
- In one review of approximately 200 pediatric cases of **condylomata acuminata** in which HPV **6 or 11** was detected in **56%**, HPV **1 to 4** in **12%**, and HPV **16 or 18** in **4%**
- A separate series in which 40 children **under the age of 12** with condyloma acuminatum underwent wart excision and HPV testing found that HPV types **6, 11, and/or 16** were present in only **one-third** of cases

Genital warts(Condyloma acuminatum)

- External anogenital warts can be accompanied by involvement of the **cervix or urethra**
- CA may also develop in the **anal canal**, typically manifesting as small flat-topped to globoid-shaped papules, usually distal to the dentate line

Genital warts(Condyloma acuminatum)

- **CLINICAL COURSE:**
- increase in number and size or regress spontaneously
- one-third of anogenital warts regress without treatment within **four** months
- HPV infection **may persist** despite resolution of visible warts and may result in wart recurrence
- Mechanical irritation, wounding, immunosuppression, inflammation, may predispose to reappearance

- Anogenital warts 90% are caused by **nononcogenic HPV types 6 or 11**. HPV types **16, 18, 31, 33, and 35** also are occasionally identified in anogenital warts (usually as co-infections with HPV 6 or 11) and can be associated with foci of high-grade squamous intraepithelial lesion (**HSIL**), particularly among persons who have **HIV infection**.

- SQUAMOUS CELL CARCINOMAS ARISING IN OR RESEMBLING ANOGENITAL WARTS MIGHT OCCUR MORE FREQUENTLY AMONG IMMUNOSUPPRESSED PERSONS, THEREFORE REQUIRING BIOPSY FOR CONFIRMATION OF DIAGNOSIS FOR SUSPICIOUS CASES

- High-Grade Squamous Intraepithelial Lesions: BIOPSY OF AN ATYPICAL WART MIGHT REVEAL HSIL OR CANCER OF THE ANOGENITAL TRACT.

بیماریهایی که HPV در مخاط سر و گردن:
دهان، حلق، حنجره و مجاری تنفسی ایجاد
می کند

- The history of HPV in head and neck site starts in 1901 when the contagious transmission of warty lesions into the mouth via oral sex was described
- During the following decades, HPV was associated with development of laryngeal warts, koilocytotic atypia and head and neck cancer

Recurrent Respiratory Papillomatosis(Laryngeal Warts)

JoRRP

- Transmission: during birth from the mother as the fetus passes through an infected genital tract
- Prevalance: 4.5 in 100000 child
- **Laryngeal papillomas** usually manifest with progressive hoarseness, stridor, severe airway obstruction
- HPV 6, 11
- multiple surgical debulking procedures are needed
- papillomatous lesions can, rarely, grow aggressively, spread into the lungs, and undergo malignant transformation

AoRRP

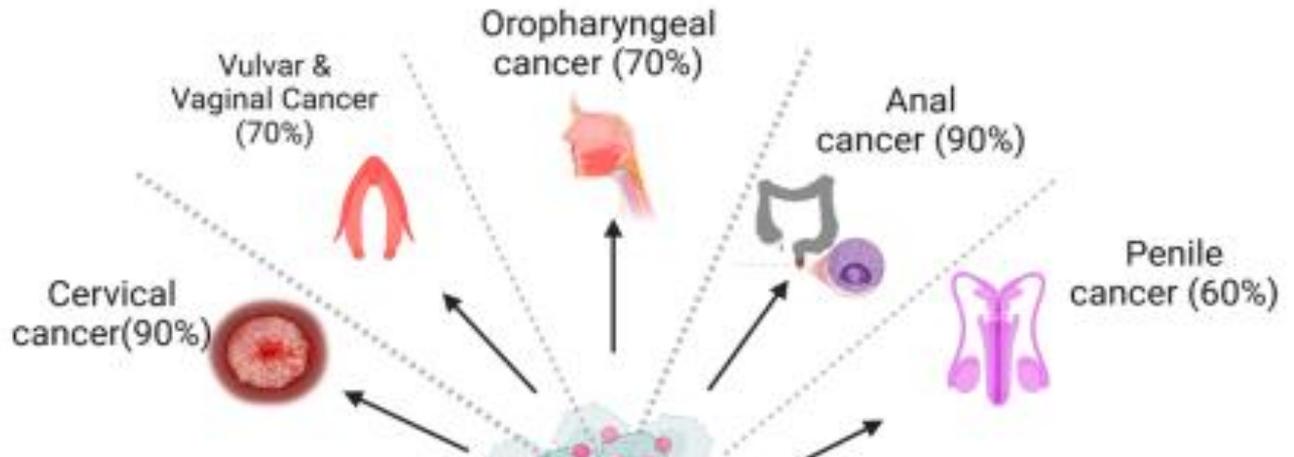
- after 20 years of age in the **third and fourth** decades of life
- more commonly in **men**
- In adults HPV is transmitted sexually, through oral contact with infected external genitalia
- hoarseness is the most common finding
- In this form, the papillomas are often solitary, they do not usually spread, and recur less frequently than those seen in the juvenile form

HPV and cancer

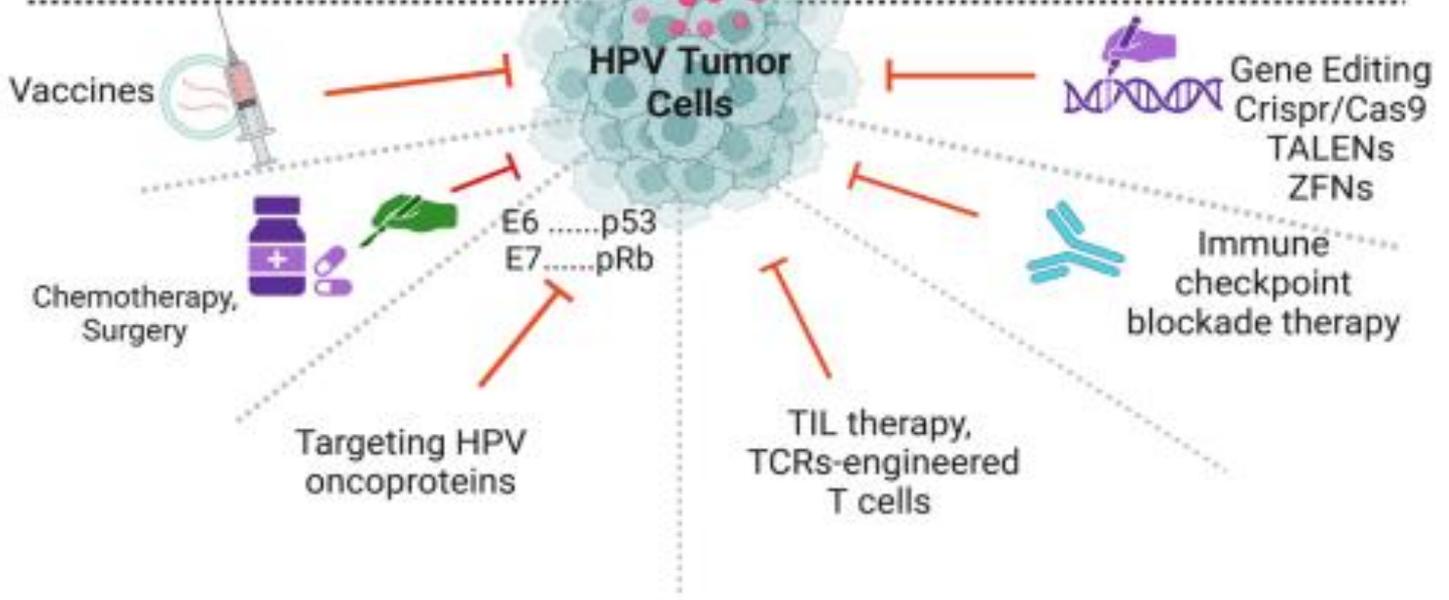
Now, HPV has been recognized by WHO as the causative agent of **several cancers**. About **5%** of all malignancies in humans, including those of the **cervical, vulvar, vaginal, penile, anal, head and neck cancers, particularly oropharyngeal** regions and oral cavity, are caused by HPV.

The main contributors to HPV-related malignancies are the virus's **persistent infection** and the activity of its **oncogenes**.

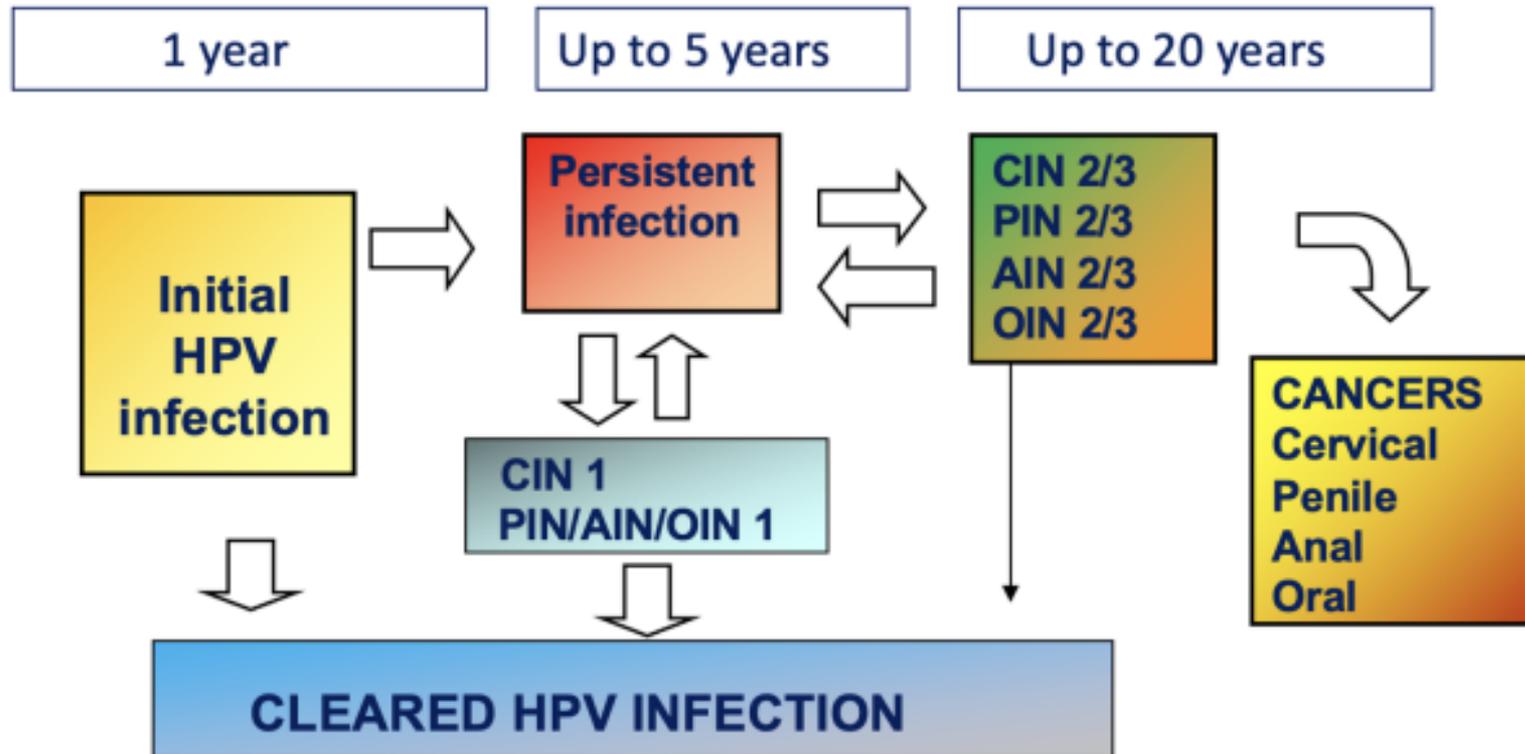
Various HPV related Carcinoma



Therapeutic Approaches



Natural History of HPV Infection and Cancers



CIN: cervical intraepithelial neoplasia; PIN: penile intraepithelial neoplasia; AIN: anal intraepithelial neoplasia; OIN: oral intraepithelial neoplasia.

HPV and cancer

High-risk HPV strains, particularly **HPV-16** and **HPV-18**, are responsible for over 70% of cervical cancer cases worldwide, as well as a significant proportion of other genital and head and neck cancers.

At the molecular level, the oncogenic activity of these viruses is driven by the **overexpression of E6 and E7 oncoproteins**. These oncoproteins **dysregulate the cell cycle**, **inhibit apoptosis**, and promote the **accumulation of DNA damage**, ultimately transforming normal cells into cancerous ones.

Due to the lack of noticeable symptoms, HPV infection often appears to be **clinically asymptomatic**, yet a few lesions that may develop into invasive malignancies can be seen in the genital organs.

Precancerous lesions and cancer of cervix

- fourth most common cancer among females
- Virtually **all cases** of cervical cancer are attributable to HPV infection
- HPV **16 and 18** accounting for the majority of cancers



Vulvar and vaginal cancer

- uncommon globally
- **not** all cancers of the external genitalia are associated with HPV infection

Vulvar and vaginal cancer

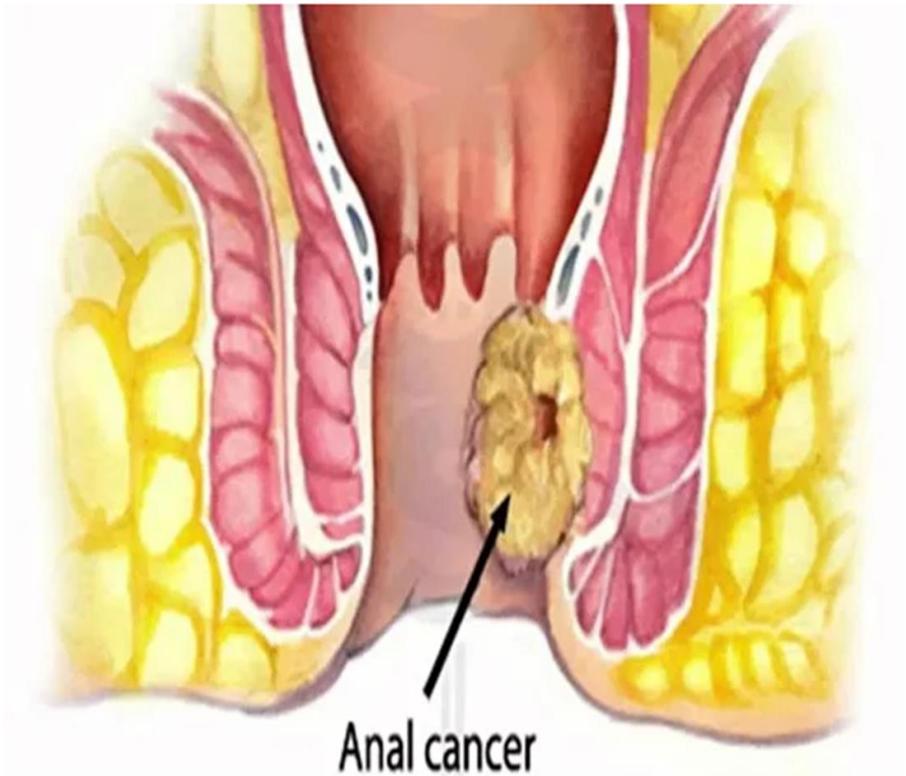
- attributable fraction:
 - 29 to 43%: vulvar cancer,
 - 87%: VIN,
 - 70 %: vaginal cancer,
 - 69 to 100%: VAIN
- HPV types 16 and 18:
 - 35 to 77% of HPV-positive vulvar cancer,
 - 75 to 80% of HPV-positive precancerous vulvar lesions,
 - 60% of HPV-positive vaginal cancer and precancerous vaginal lesions

Vulvar and vaginal cancer

- HPV-associated vulvar cancers:
 - younger age,
 - basaloid instead of keratinizing pathology,
 - do not have p53 mutations,
 - associated with sexual risk factors

Anal cancer

- Anal cancer is becoming more common in both genders
- **Almost all** squamous cell carcinomas of the anus are caused by HPV and are preceded by HSIL, which are screening-detectable precancerous lesions



Anal cancer

- Although rare among the general population, anal cancer disproportionately affects several specific populations, including **people with HIV (PWH), men who have sex with men**
- **(MSM), solid organ transplant recipients (SOTR), and women with a history of vulvar cancer or precancer**

Anal cancer

- HPV types **16 and 18** cause nearly **90%** of anal cancers and precancerous anal lesions (ie, HSIL)
- HPV **16** is the most frequently isolated type in anal malignancies
- HPV **16** presence is also associated with a better prognosis(in male patients)

آیا برای کانسرهاى آنال مرتبط با HPV هم
برنامه غربالگرى وجود دارد؟

International Anal Neoplasia Society's consensus guidelines for anal cancer screening

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TABLE 1 Populations for screening.

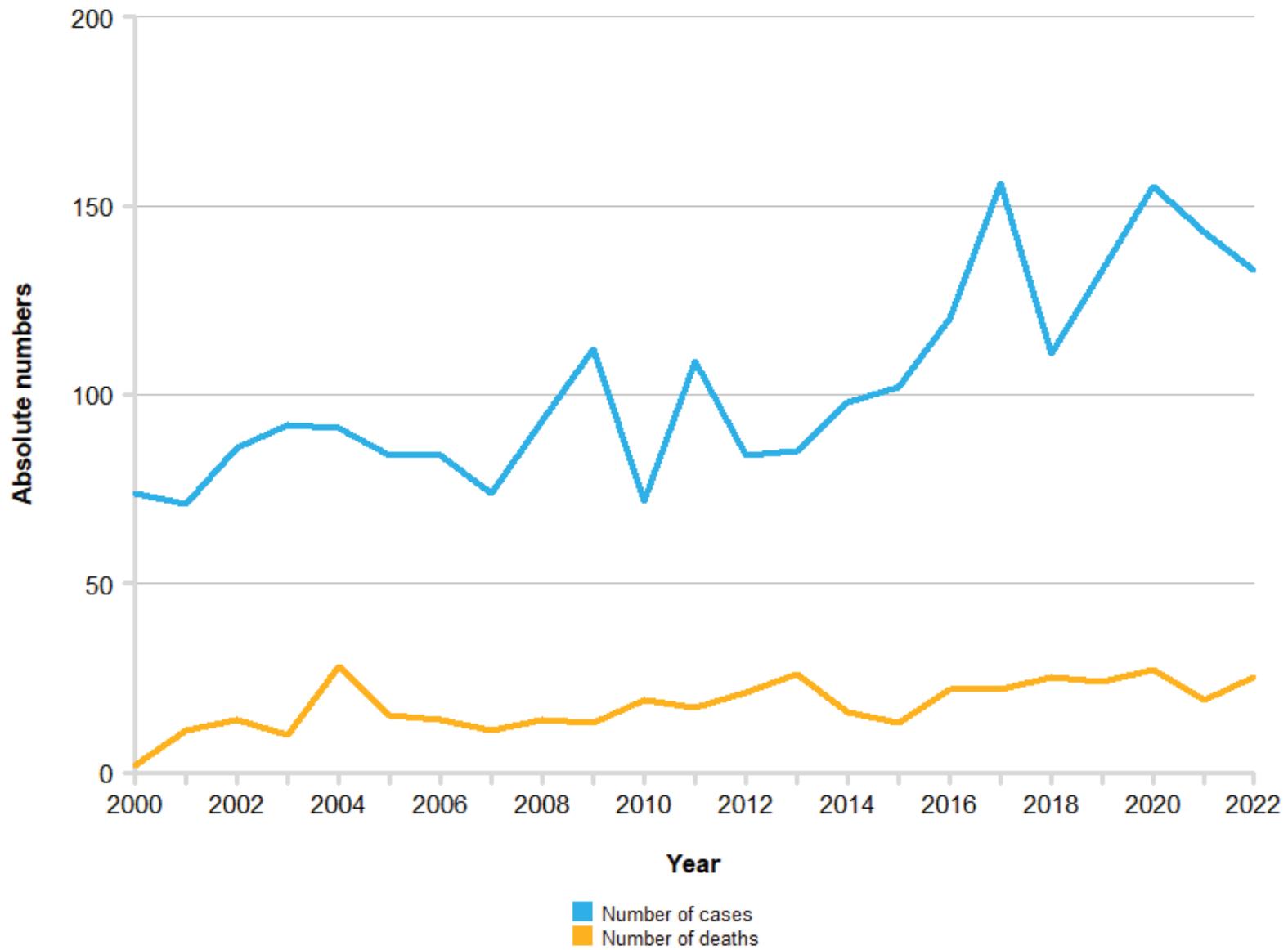
Population—Risk category	When
Risk Category A (incidence \geq 10-fold compared to the general population)	
MSM and TW with HIV	Age 35
Women with HIV	Age 45
MSW with HIV	Age 45
MSM and TW not with HIV	Age 45
History of vulvar HSIL or cancer	Within 1 year of diagnosis
Solid organ transplant recipient	10 years post-transplant
Risk Category B (incidence up to 10-fold higher compared to the general population)	
Cervical/vaginal cancer	Shared decision age 45 ^a
Cervical/vaginal HSIL	Shared decision age 45 ^a
Perianal warts (male or female)	Shared decision age 45 ^a
Persistent cervical HPV 16 (> 1 year)	Shared decision age 45 ^a
Other immunosuppression (e.g., Rheumatoid arthritis, Lupus, Crohn's, Ulcerative colitis, on systemic steroid therapy)	Shared decision age 45 ^a

Screening method for anal cancer?

- Anal cytology, hrHPV testing (including genotyping for HPV16), and hrHPV-cytology co-testing
- High resolution Anoscopy
- In the absence of HRA availability, screening should be limited to digital anal rectal exam (DARE) for detection of anal cancer

Penile cancer

- Penile cancer, with an average annual incidence of **1 per 100,000** men, is a rare malignancy
- The mean age at diagnosis is 72 years and around 7% of all men diagnosed with penile cancer are diagnosed before the age of 40



Penile cancer

- Recent observations suggest a rise in cases among **younger individuals**, possibly linked to changes in sexual behaviors leading to increased exposure to STD and higher rates of **HPV infection**
- Squamous cell cancer (SCC) is the most common type

Penile cancer

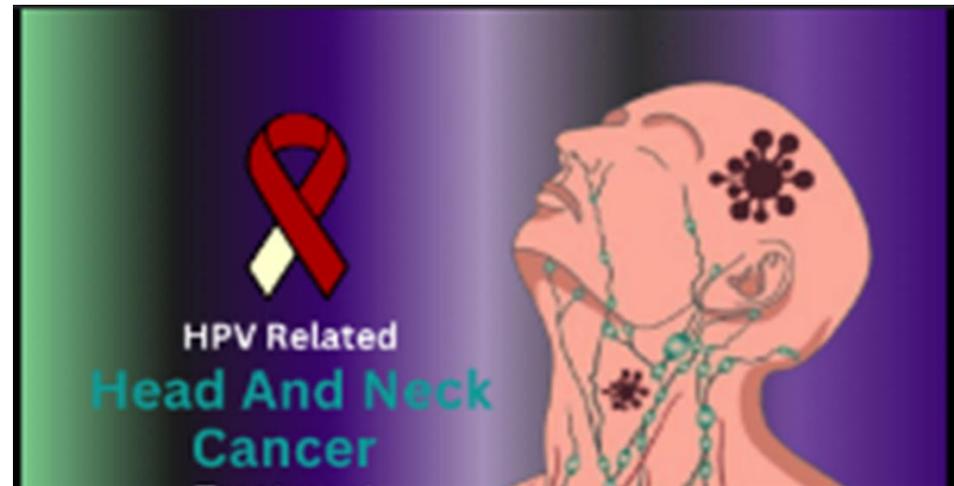
- HPV-associated penile cancers occur at a **younger age**, exhibit **basaloid** instead of keratinizing pathology, do **not** have **p53** mutations, and are associated with sexual risk factors
- Studies suggest approximately **40%** of penile cancers and **79.8% of penile intraepithelial neoplasia HPV-positive**
- HPV types **16 and 18** are the most commonly detected in penile cancer cases, with both types present together in about one-third of cases

Penile cancer

- In penile intraepithelial neoplasia (PeIN), known as a precursor lesion of penile SCC, HPV positivity rate increases with higher grades of dysplasia
- Uncircumcised men have higher HPV prevalence and it seem like circumcision protects against HPV and HPV-related penile cancer
- The prognostic significance of HPV in penile cancer, remains an area of research interest

Neoplastic diseases of head and neck

- HPV has been hypothesized to play a role in the etiology **HNSCC** since many decades ago, in particular as early as **1983**



Neoplastic diseases of head and neck

- while **tobacco** and **alcohol** were historically the main drivers of head and neck cancers, in the past several decades, the proportion of head and neck cancers attributable to **HPV** has increased dramatically worldwide, notably **OPSCC**
- The burden of HPV-positive OPSCC is significantly higher in **males** from more developed countries

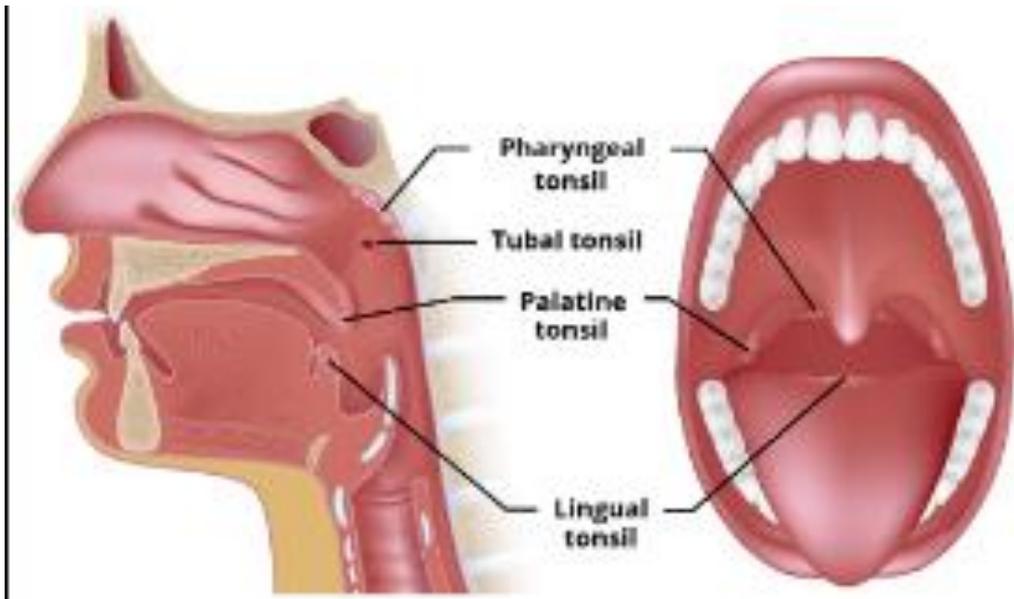
Neoplastic diseases of head and neck

- HPV prevalence was 35.6% in **oropharyngeal** cancers, 23.5% in **oral cancers** and 24.0% in **laryngeal** cancers,
- overall prevalence of HPV in HNSCC was estimated at **26%**



- Half of HNSCC cases in the US are caused by infection with **high-risk HPV**
- HPV-16 and HPV-18 subtypes contribute to the majority (85%) of HPV-related HNSCC
- while the remaining 15% of HPV-related HNSCC are mostly caused by HPV-**33**, HPV-**35**, HPV-**52**, HPV-**45**, HPV-**39** and HPV-**58**

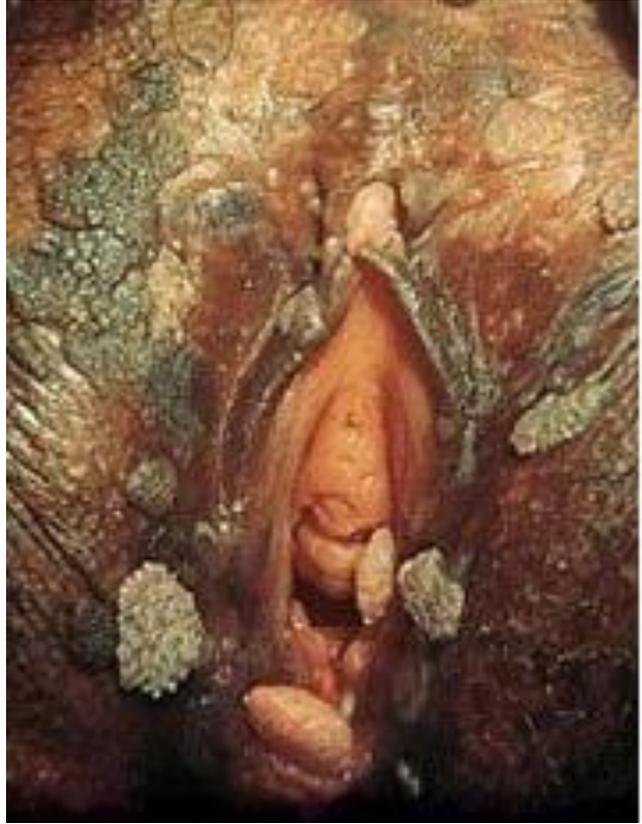
- The oropharynx is the most common site of head and neck cancer attributable to HPV. In particular, **palatine tonsil** and the **base of the tongue**



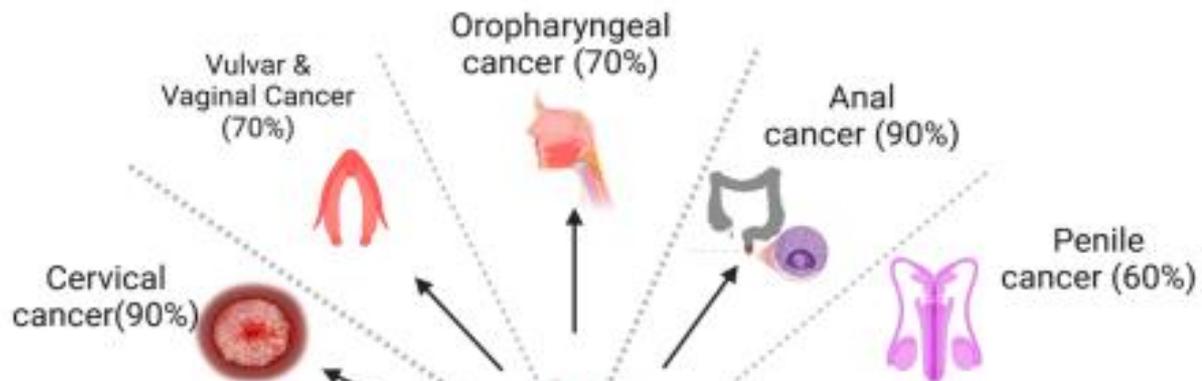
- HPV-related oropharyngeal cancers occur in a **younger** population and are associated with sexual risk factors
- ☆ **Oral SCC** is currently the most frequent HPV-driven cancer in the USA even **more than cervical cancer** in females!
- HPV oral infections occur more frequently in **males**
- oropharyngeal cancer mostly occurs in **male** patients

- HPV-positive OSCCs present a **better prognosis** than HPV-negative OSCCs
- HPV-positive OPSCCs tend to present with large metastases in the cervical lymph nodes, with a clinically and radiologically occult primary, allowing an **earlier diagnosis** and, therefore, a **different prognosis**.

- The mortality risk of patients with HPV-associated OSCCs is **50% lower** in comparison to patients with HPV-negative OSCC, mostly due to **improved locoregional control** and **increased radiation sensitivity**



Various HPV related
Carcinoma



Therapeutic Approaches

