In the name of **God**

HPV

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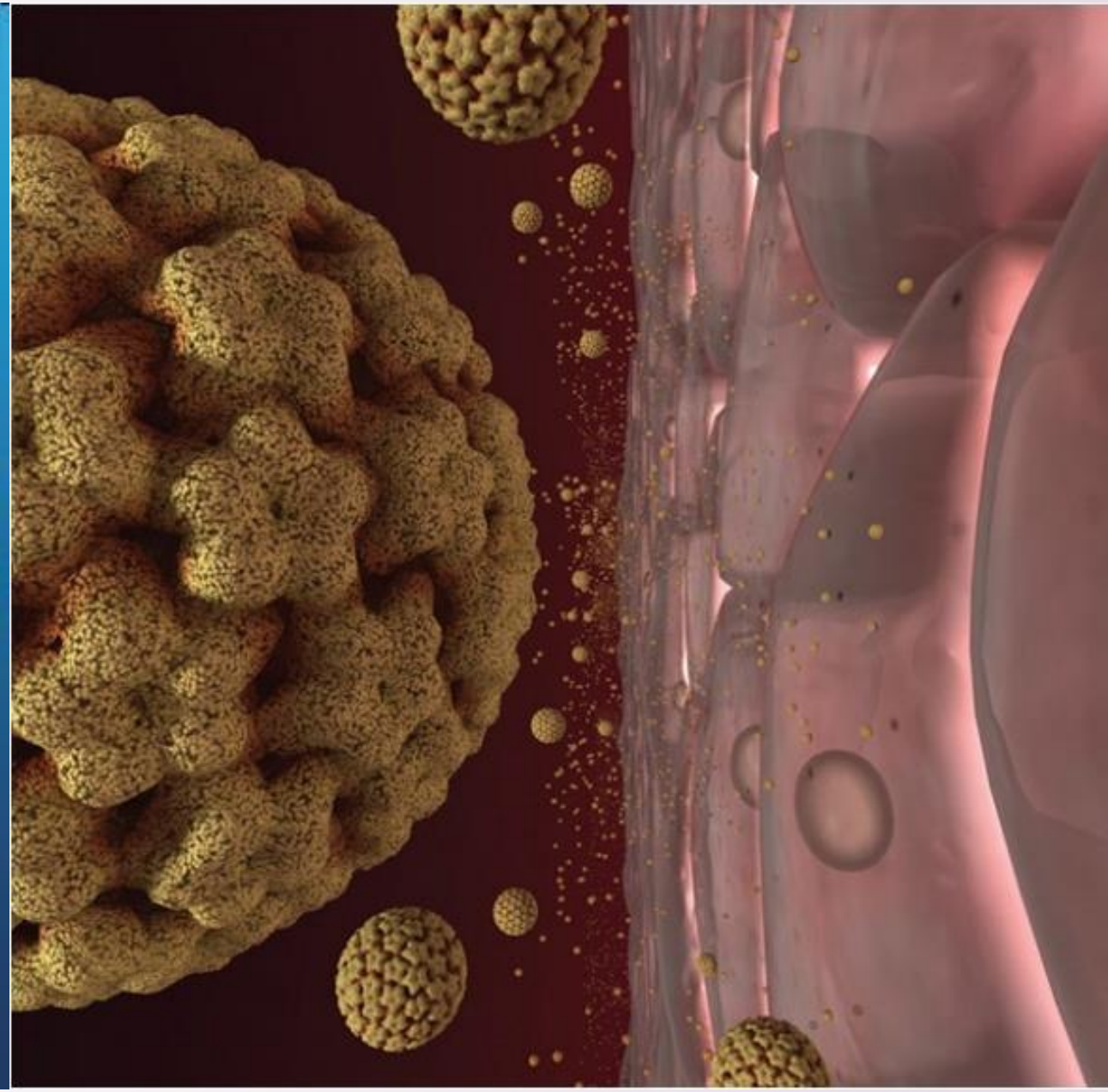
- *Human papillomaviruses* (HPVs) are widespread throughout the population, produce **epithelial tumors** of the skin and mucous membranes, and have been closely associated with **genital tract malignant** diseases.
- The infectious nature of human warts was initially seen in the late 19th century when human wart extracts were shown to produce warts with injection into humans.

- Papillomaviruses constitute the *Papillomavirus* genus of the Papillomaviridae family.
- They are **nonenveloped** viruses that are 55 nm in diameter and have an icosahedral capsid composed of 72 capsomeres that enclose a double-stranded circular DNA genome.



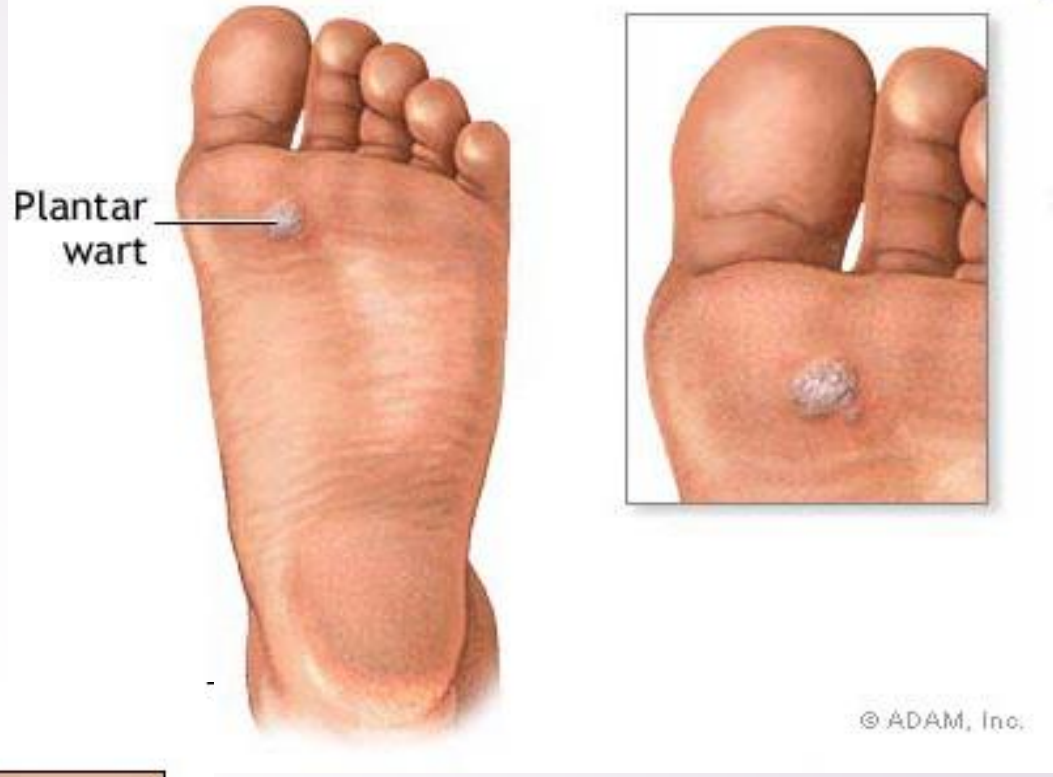
DISEASE	HPV TYPES[a] FREQUENT ASSOCIATION	HPV TYPES[a] LESS FREQUENT ASSOCIATION
Plantar warts	1, 2, 27	4, 26,[b] 28, 29, 41,[c] 57, 63, 65, 77,[c] 117,[b] 125,128, 129, 130, 131, 132, 133, 148, 149, 179, 184
Common warts	1, 2, 4, 27	
Common warts of meat, poultry, and fish handlers	2, 7	1, 3, 4, 10, 28
Flat and intermediate warts	3, 10	27,[b] 28, 38, 41,[c] 49,[b] 75, 76, 126[b]
Epidermodysplasia verruciformis	5,[c] 8,[c] 9, 12, 14,[c] 15, 17[c]	19, 20,[d] 21, 22, 23, 24, 25, 36, 37, 38, 47,[c] 49, 50, 75, 93
Condylomata acuminata	6, 11	16,[c] 18,[c] 26,[c] 31,[c] 33,[c] 35,[c] 40, 42, 43, 44, 45,[c] 51,[c] 52,[c] 53,[c] 54, 55, 56,[c] 58,[c] 59,[c] 66, 68,[c] 70, 153, 175, 178, 180, 200, 201, 202
Intraepithelial neoplasia, unspecified		26,[c] 30,[c] 34, 39,[c] 40, 53,[c] 57, 59,[c] 61, 62, 67,[c] 68,[c] 69, 71, 81, 83
Low grade	6, 11	16,[c] 18,[c] 31,[c] 33,[c] 35,[c] 42, 43, 44,[d] 45,[c] 51,[c] 52,[c] 54, 61, 70, 72, 74[b]

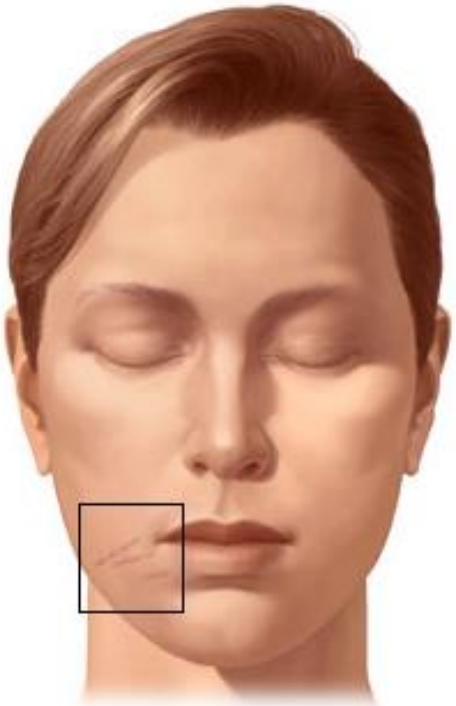
High grade	16,[c] 18[c]	6, 11, 31,[c] 33,[c] 34,[b] 35,[c] 39,[c] 42, 44, 45,[c] 51,[c] 52,[c] 56,[c] 58,[c] 66,[c] 67[c]
Cervical carcinoma	16,[c] 18[c]	26,[c] 31,[c] 33,[c] 35,[c] 39,[c] 45,[c] 51,[c] 52,[c] 56,[c] 58,[c] 59,[c] 66,[c] 67,[c] 68,[c] 73,[b,c] 82[c]
Recurrent respiratory papillomatosis	6, 11	16,[c] 18,[c] 31,[c] 33,[c] 35,[c] 39[c]
Focal epithelial hyperplasia of Heck	13, 32	18,[c] 33,[c] 45[c]
Conjunctival papillomas and carcinomas	6, 11, 16[c]	
Other cutaneous lesions[e]		26,[b,c]36, 37, 38,[c] 41,[c] 48,[b,c] 60, 72,[b] 88, 92, 93, 94, 95, 96, 107, 110, 111, 155, 174, 197[c]
Other genital lesions		26,[b,c] 30,[c] 84,[c] 85, 86,[c] 87, 89, 90, 91, 97, 101, 102, 103, 106, 175, 180, 199
Healthy cutaneous or mucosal tissue		80, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 127, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 150, 151, 156, 157, 158, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 199, 205, 209

Incidence and Prevalence

- **Three** types of cutaneous HPV infections are widespread throughout the general population.
- **Common** warts, which represent up to 71% of all cutaneous warts, occur frequently among **school-aged** children, with prevalence rates of 4% to 20%
- Although less common (34% of cutaneous warts), **plantar** warts are observed frequently among **adolescents** and **young adults.**

- **Juvenile** or **flat** warts are the least common of the three types (4%) and occur predominantly in **children**.
- Other groups at **high risk** for the development of cutaneous warts include **butchers**, **meat packers**, and **fish handlers**





Flat warts:
Found on face, neck, arms, back of hands, and legs

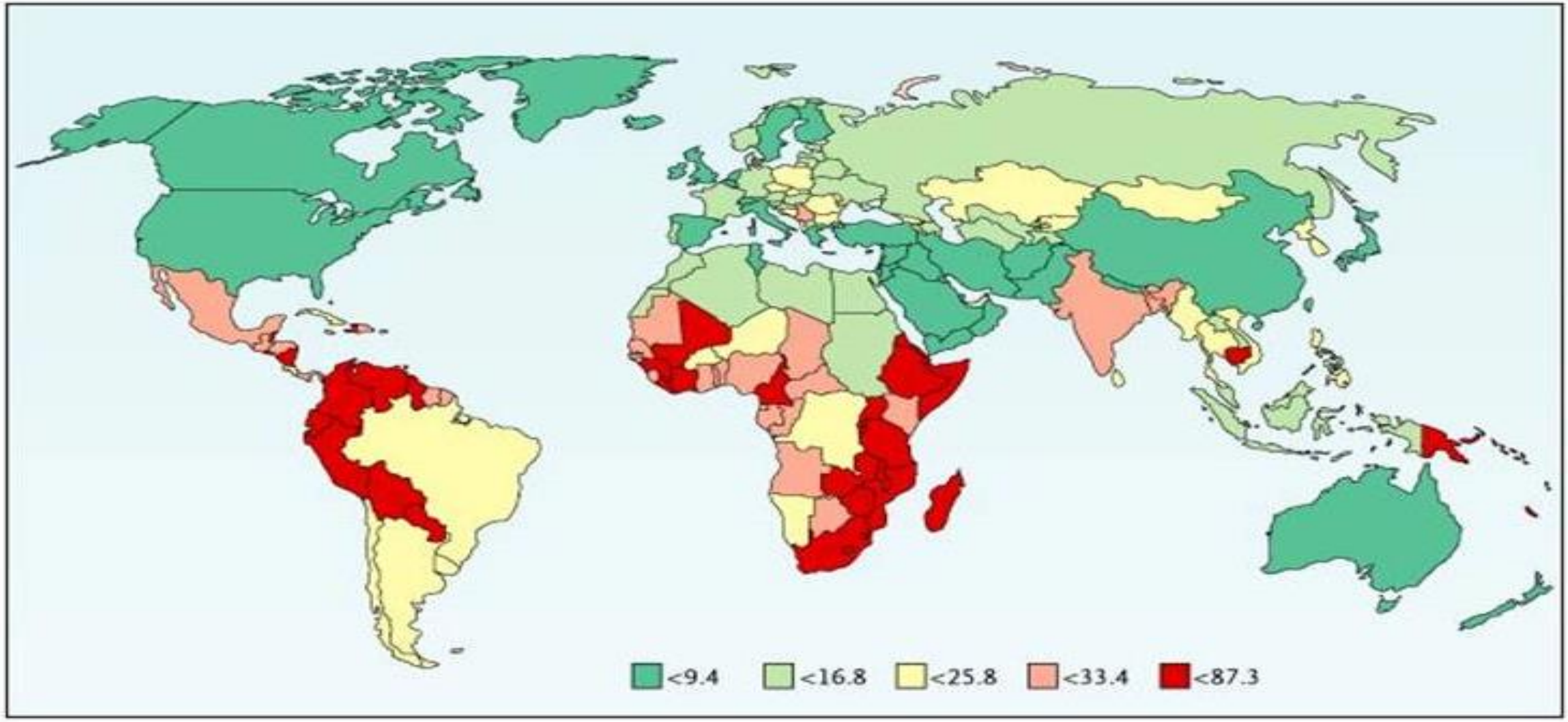
- **Epidermodysplasia verruciformis** is a rare, typically **autosomal recessive** condition characterized by the appearance early in life of **disseminated** cutaneous warts and frequent **malignant** transformation.
- Large surveys in the United States have shown that the **prevalence** of any and **high-risk** genital HPV in 18- to 59-year-olds was 45.2% and 25.1% in males, and 39.9% and 20.4% in females, respectively

- **Peak** prevalence was reached in the age-class **25 to 29** years in **males** and essentially remained unchanged in the older groups. In **females** the peak prevalence was in the **20- to 24-years** age-group

- The **incidence** of the disease has **risen**. The annual number of initial visits to physicians' offices for genital warts **doubled** between 2000 and 2014, from 220,000 to 465,000.
- HPV infection of the cervix gives **rise** to the **most common** cause of **squamous cell abnormalities** on Papanicolaou (Pap) smears and are found in **two-thirds** of 1000 females aged 15 to 39 years.

- The prevalence of **oral** HPV infections is 7.5%, but that of **associated lesions** is 0.5%, although **higher** in **human immunodeficiency** virus (HIV)-infected subjects, particularly on **highly active** antiretroviral therapy

Incidence of Cervical Cancer Worldwide



Transmission

- **Close** personal **contact**, especially within the family and school class, is likely to be important for the transmission of most cutaneous warts
- **Minor trauma** at the site of inoculation may also be important, as suggested by the high frequency of disease among **meat handlers**.

- **present**, or **recent** sexual partners; the **frequency** of sex or other intimate **skin-to-skin** contact; and the **sexual histories** or behavior of sex **partners** are **risk factors** of genital HPV transmission, whereas **circumcision** in some studies has been found to be **protective**, as with HIV and herpes simplex virus (HSV)
- Young children may acquire genital warts from **hand** contact with **nongenital** lesions.

- Approximately **one-fifth** of prepubertal children with condyloma acuminatum have HPV **type 1 or 2** in the lesions.
- **HPV-6** DNA has been identified in **cutaneous** warts of **family** contacts of children with **anogenital** warts
- **Recurrent respiratory** papillomatosis in young children is thought to be acquired via passage through an infected **birth canal** or through the **placenta**.

- In addition, neonates are more likely to **harbor** HPV DNA in the **oral** cavity if the **cervix** of the mother contains HPV DNA.
- Although the **median** age of onset of **recurrent respiratory** papillomatosis is **3** years, cases have been documented at birth, **even after cesarean section**

- The role of **cesarean section**, if any, in prevention of transmission is **unknown**, and the procedure is **not** recommended for that purpose.
- In the **adult-onset** form **recurrent respiratory** papillomatosis is associated with a higher-than-expected number of lifetime sexual partners and with **oral-genital** contact.

- **nosocomial** transmission appears possible because infectious virus can be recovered from the **fumes** released from lesions during treatment with a **carbon dioxide (CO2) laser** or **electrocoagulation**.
- HPVs are **resistant** to heat, and use of an **autoclave** is probably necessary for **sterilization** of contaminated instruments

HPV and Malignant Diseases

- Observations of patients with **epidermodysplasia verruciformis** provided the **initial** evidence that suggested that HPVs might also be **carcinogenic**.
- Most research investigating the oncogenic potential of HPVs has focused on **genital tract malignant** diseases.

- The **low** prevalence of cancer of the uterine cervix among Catholic **nuns**, the **direct** association of risk with **number** of sexual partners, and the **increased** risk of malignant disease that is associated with a **male sexual partner** whose **previous consort** had cervical cancer have been observations consistent with a **sexually transmitted agent** playing a role in the pathogenesis of **cervical cancer**

- The association between those HPV types called **high-risk** oncogenic (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66, as classified by the International Agency for Research on Cancer) and **cervical cancer** is **strong**
- For the **most** oncogenic of these viruses, **HPV-16** for squamous cell carcinoma (**SCC**) and **HPV-18** for **adenocarcinoma**

- In a worldwide survey **HPV DNA** was found in **99.7%** of cervical cancer samples
- HPV is found in 91% of **anal SCCs** and, for the period 2005–09, in 72% of **oropharyngeal SCCs**.
- The fraction of **SCCs** attributable to HPV is 69% for the **vulva**, 75% for the **vagina**, and 63% for the **penis**.

- Before 2000, only 40.5% of oropharyngeal SCCs were associated with HPV. HPV-associated **oropharyngeal** cancer is now **more** common than cervical cancer in the United States.
- mucosal **high-risk HPVs** have been found in cancers of the **esophagus**, **lung**, and **breast** but also of the **colon**, **urothelium**, **prostate**, the **ovary**, and **endometrium**, thus raising a possible causal role in these tumors

- **HPV-16** has been found in some SCCs of the **conjunctiva** and of the **nail** bed
- The **beta** HPV types found in the SCCs of patients with **epidermodysplasia verruciformis** have also been found in about **a third** of **keratinocyte carcinomas** (SCCs and basal cell carcinomas) in immunocompetent hosts and in up to 80% of immunosuppressed hosts.

- between 15% and 30% of women with **normal** cervical cytology but **high-risk** HPV infection have cervical intraepithelial neoplasia (CIN) grades 2 or 3 develop in the **following 4 years**.
- Although **clearance** of HPV DNA appears to precede clearance of cervical lesions, **persistence** of HPV DNA after treatment for CIN 2 or 3 is a predictor of **relapse**.

- The **number** of sexual partners, the **age** of **first** sexual intercourse, and the **sexual behavior** of the **husband** are **risk factors** for HPV infections and also for cervical cancer, which occurs later in life.
- In some studies a direct association is found between **viral load** and the risk of **cancer**, which is consistent with a biologic gradient.

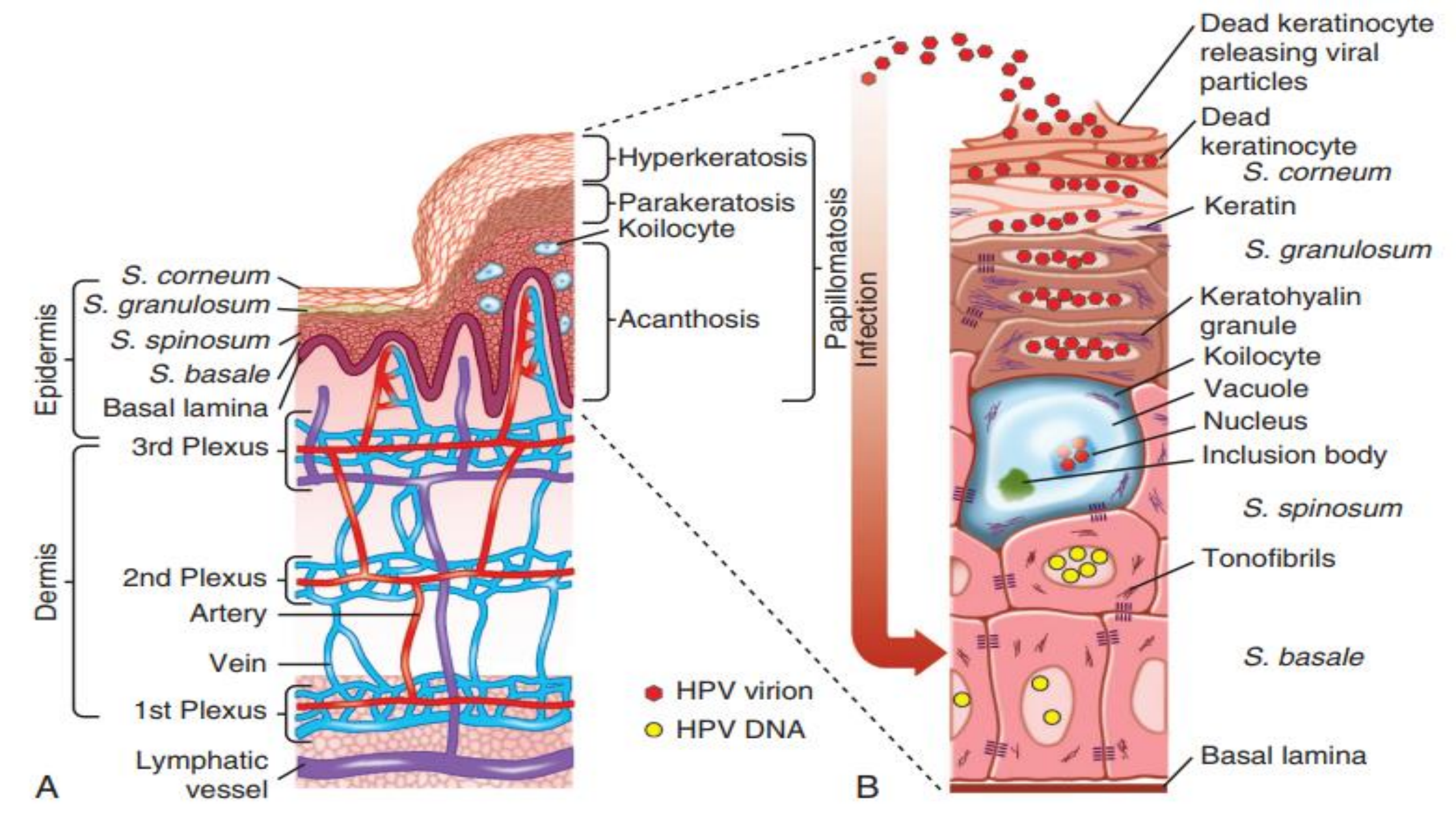
- Other **alternative risk factors** for **cervical cancer**, such as the use of oral contraceptives, high parity, tobacco smoking, nutrition (vitamins C and E, carotenoids), immunosuppression, prior HSV-2 or *Chlamydia trachomatis* infection, **have not** reached the strength and coherence of the evidence gathered for HPV.

CLINICAL MANIFESTATIONS

- ***Cutaneous*** *warts* include **deep plantar warts**, **common** warts, and **plane** or **flat** warts.
- ***Deep plantar warts*** *(verrucae plantaris)* affect mostly **adolescents** and **young adults**. The lesions **characteristically** look like deep-seated, raised bundles of soft keratotic fibers 2 mm to 1 cm in diameter; shaving reveals punctate, bleeding blood vessels.

- These lesions are often **painful** and may also be located on the **palms** of the hands.
- ***Common*** *warts (verrucae vulgaris)* appear as well-demarcated, exophytic, hyperkeratotic papules with a rough surface. They may occur on the **dorsum** of the hand, between the fingers, around the nails (periungual warts), on the palms or soles, or, rarely, on mucous membranes. Warts may coalesce and reach a diameter of 1 cm.

- ***Plane*** *warts (verrucae planae)* are commonly found on **children** and appear as **multiple**, slightly elevated papules with an irregular contour and distribution and a smooth surface. They occur on the face, neck, and hands.
- Cutaneous warts are usually **asymptomatic**, although they may **bleed** and can be **painful** when located over **weight-bearing** surfaces or points of friction.


Epidermis
Dermis
S. corneum
S. granulosum
S. spinosum
S. basale
Basal lamina
3rd Plexus
2nd Plexus
Artery
Vein
1st Plexus
Lymphatic vessel
A
Hyperkeratosis
Parakeratosis
Koilocyte
Acanthosis
Papillomatosis
Infection
HPV virion
HPV DNA
Dead keratinocyte releasing viral particles
Dead keratinocyte
S. corneum
Keratin
S. granulosum
Keratohyalin granule
Koilocyte
Vacuole
Nucleus
Inclusion body
S. spinosum
Tonofibrils
S. basale
Basal lamina
B

- **Anogenital Warts** *Anogenital warts* are flesh colored to gray colored, hyperkeratotic, exophytic papules, either sessile on the skin or, more frequently, attached by a short, broad peduncle
- Lesions **range** from smooth, pearly papules to more jagged, acuminate growths. They **vary** in size from less than a millimeter in diameter to several square centimeters when they merge into plaques.

- In **uncircumcised** men the **preputial cavity** is involved in 85% to 90% of cases
- In the United States, where about 85% of the male population is circumcised, the **penile shaft** is the most common site of lesions. The **urethral meatus** is also involved in 1% to 25% of patients.

- Involvement of the **perianal** area varies according to sexual practice, from very high among **MSM** (about 10%, and double with **HIV** seropositivity) to low among heterosexual men.

- In women **most** lesions are distributed over the **posterior introitus** and, to a **lesser** degree, over the **labia majora** and **minora** and the **clitoris**
- In order of **decreasing frequency**, the perineum, vagina, anus, cervix, and urethra each represent less than **one-quarter** of the sites of involvement

FIG. 143.2 Vulvar condylomata acuminata. *(From Gagné H. Colposcopy*

- **Typically**, these lesions are shiny white patches with geographic borders and an irregular surface that contains characteristic capillary loops.
- The presence of external genital warts may indicate the existence of cervical HPV squamous epithelial lesions, including CIN
- About **three-quarters** of patients with anogenital warts are **asymptomatic**.

- Genital HPV infections may also belong to the **spectrum** of penile, anal, vulvar, vaginal, and cervical intraepithelial neoplasias (PIN, AIN, VIN, VAIN, and CIN, respectively)
- Histologically, **pigmented papules** of the external genitalia may show evidence of **intraepithelial neoplasia**. This clinicopathologic entity is called ***bowenoid papulosis***

FIG. 143.3 Pigmented penile warts mimicking bowenoid papulosis.
(From Habit TP, ed. Clinical Dermatology. *4th ed. London: Mosby; 2004.)*

- *Bowenoid papulosis* can evolve to ***Bowen*** *disease*, which manifests as a flat red-to-brown plaque with well-demarcated borders and a scaly irregular surface. On the glans penis the lesion is known as ***erythroplasia of Queyrat***.
- **HPV-16** and **HPV-18** have been recovered from both ***bowenoid*** *papulosis* and ***Bowen*** *disease.*

- the **outcome** (regression, no change, or progression) is highly **variable** and **depends** on the histologic grade of the tumor, the HPV type, and the method of diagnosis (conization, punch biopsy, or scraping).
- **CIN grade 1** lesions have an approximate probability of **60%** to **regress**, **30%** to remain **unchanged**, **10%** to progress to **CIN 3**, and **1%** to progress to **invasive cancer**. For **CIN 2** the figures are **40%, 40%, 20%**, and **5%**, respectively

- The risk of progression to cancer is the highest with **CIN 3** at **12%**; only **a third** of these lesions disappear spontaneously.
- the presence of **perianal** warts or anal symptoms in association with a history of **anal** sexual play or intercourse should prompt a **digital rectal examination** and an **anoscopic** evaluation. In the general population a history of anal warts increases by about **10 times** the risk of **anal cancer**.

DIAGNOSIS

- The diagnosis of warts is usually made **clinically** with physical examination. Exophytic warts have a **characteristic** appearance.
- Although initially designed for the evaluation of the female internal genital tract, the **colposcope**, with prior application for 3 to 5 minutes of a 3% to 5% **acetic acid** solution, has become an important diagnostic tool for other HPV infections as well.

- Lesions of the external genitalia that are pigmented, appear as plaques, bleed, or are large should have **biopsies** to establish the diagnosis and **rule out** malignancy. **Biopsy** is also indicated to **confirm** the diagnosis of **epidermodysplasia verruciformis** and to determine the cause of lesions of the **oral** cavity and **upper airways**.

- **Anoscopic** examination should be considered in patients with **perianal warts**, **anal** symptoms, or a history of receptive **anal** intercourse.
- Most intra-anal lesions are **below** the pectinate line, and sigmoidoscopy is **not** routinely indicated.

- Women with a history of **anogenital** HPV disease or whose sexual **partners** have had **anogenital** HPV disease should have a **cytologic** examination of a **cervical smear** (Pap smear), at least as part of **regular screening**.
- **Koilocytes** on a cytologic smear are the **hallmark** of HPV infection.

- Depending on the patient's **age** and the **location** and nature of the HPV **infection**, the **sensitivity** of the **Pap smear** in detection of HPV infection ranges from **30% to 90%.**
- Virus **cultivation** techniques are **not** available for the clinical diagnosis of HPV infections.

- HPV infection may elicit a **serologic** response. In patients with cutaneous warts, condyloma acuminatum, or recurrent respiratory papillomatosis, **antibodies** directed against the **viral capsid** have been detected.
- Anti-HPV **antibodies** tend to **disappear** with disease resolution but can persist for several years in asymptomatic patients

- Use of type-specific HPV DNA tests for **routine** diagnosis and management of genital warts is **not** recommended.
- HPV DNA tests FDA-approved:
- To **triage** women with **ASC-US** (atypical squamous cells of undetermined significance) Pap test results
- As an **adjunct** to Pap test **screening** for **cervical cancer** in women **30 years or older**

Thanks for your attention