

HPV – Human Papilloma Virus!



A story of fish, cancer, science, serendipity, immortal cells, ethics, social and political controversy.



HPV Talk Overview

- Building the case for a sexually transmitted cancer.
- Henrietta Lacks, cervical cancer and immortal cells (HeLa cells).
- What is HPV and where did it come from – ancient ancestors?
- How does a virus cause cancer and immortal cells in the lab?
- How to detect and prevent HPV related cancers and disease.



Sexually Transmitted Cancer?

- 1842 Professor Rigoni-Stern of Italy reports cervical cancer uncommon in unmarried women and rare in Nuns – 1950 Gagnon in Canada confirms rare in Nuns
- 1863 Virchow noted cervical cancer related to sexual behavior and number of births
 - ? of cervical trauma or infections during birth
- 1953 Rojel in Denmark notes increased cervical cancer in prostitutes
- 1973 epidemiology studies - cervical cancer associated with sexual behavior – early onset, multiple partners
- 1973 “The high risk male” and cervical cancer
 - Second wives diagnosed with cervical cancer after first wife dies of cervical cancer

What is being transmitted that is causing cancer?

- 1960s Smegma or proteins in semen? Circumcision noted to be protective
- 1960s Reid proposed chlamydia or genital herpes as contributing to cervical cancer
- 1970s Herpes virus found at higher frequency in women with pre-cancerous changes and isolated from cervical cancer cells
- 1949, 1956, 1976 pre-cancer changes in cervix associated with HPV described
- Early 1980s more sophisticated evidence pointing to HPV (DNA hybridization and blood antibody testing)

Harald zur Hausen MD

1983 discovered cervical cancer in humans is caused by certain types of papilloma viruses!

Awarded Nobel Prize in 2008

"For the discovery of the causative role of papilloma viruses in cancer of the cervix which led to the development of a successful HPV vaccine."



Cancer Caused by Infectious Agents Worldwide

Agent	Site	No. CA	% CA
<i>H pylori</i>	Stomach	592,000	5.5%
HPV	Cervix and others	561,200	5.2%
HBV, HCV	Liver	535,000	4.9%
HHV-8	Kaposi's sarcoma	54,000	0.9%
<i>Schistosoma</i>	Bladder	9,000	0.1%
HTLV-1	Leukemia	2,700	
Liver flukes	Liver / gallbladder	800	
<i>Total infection-related cancers</i>		1,900,000	18%
<i>Total cancers (for 2002)</i>		10,673,000	

DM Parkin (2006) *Int J Cancer*



Parkin et al. *CA Cancer J Clin* 2005;55:74

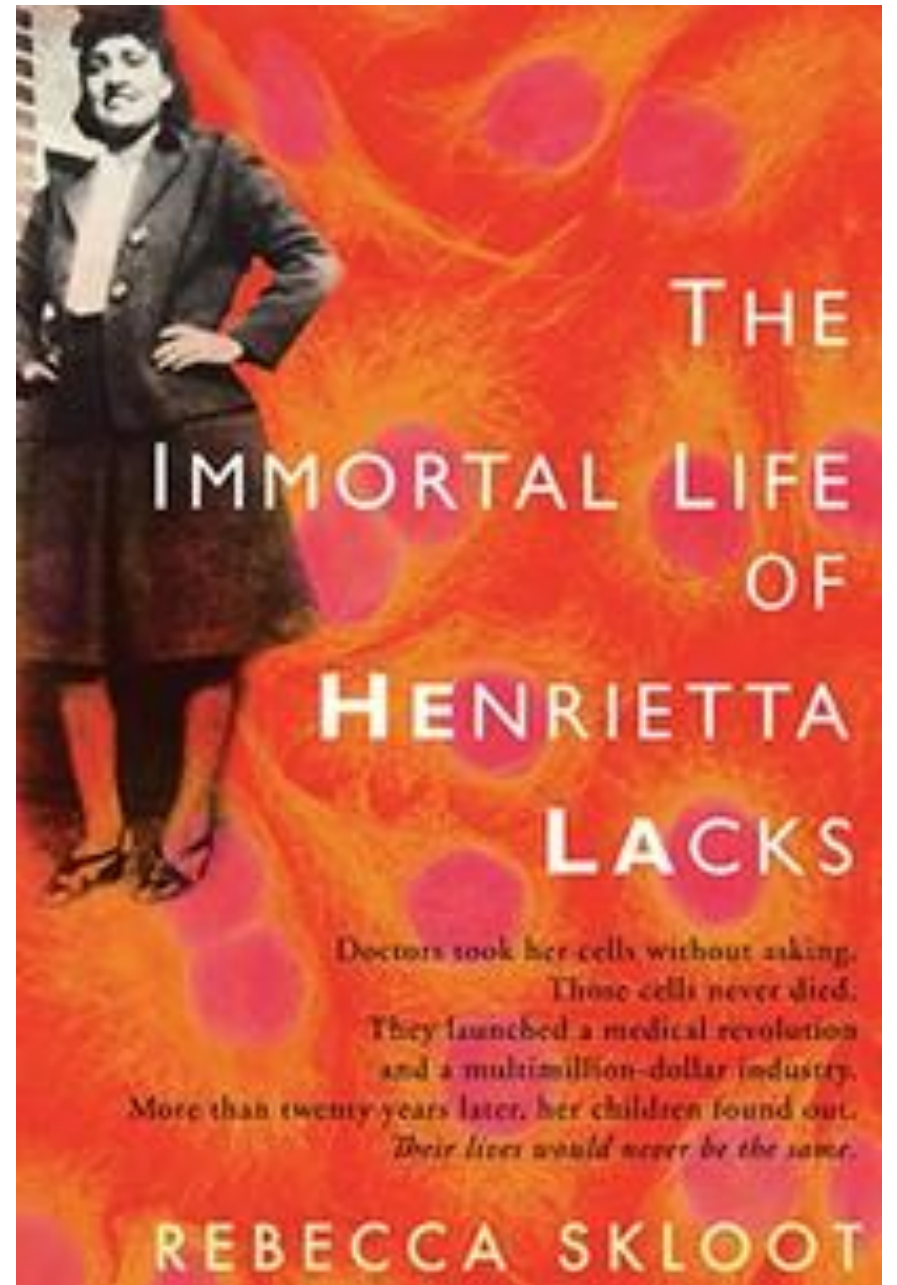
HPV causes more than half of all infection-attributable cancers in women worldwide.
And we have an effective vaccine!!!!

Meanwhile.....back in 1951:

Over 30 years before HPV was recognized as causing cervical cancer:

* Henrietta Lacks dies of an extremely aggressive cervical cancer

* unknown to her or her family, her cancer cells were taken and used in the medical research which has led to life-saving discoveries world wide





U

53

HENRIETTA LACKS (1920-1951)

Born in Roanoke on 1 Aug. 1920, Henrietta Pleasant lived here with relatives after her mother's 1924 death. She married David Lacks in 1941 and, like many other African Americans, moved to Baltimore, Md. for wartime employment. She died of cervical cancer on 4 Oct. 1951. Cell tissue was removed without permission (as usual then) for medical research. Her cells multiplied and survived at an extraordinarily high rate, and are renowned worldwide as the "HeLa line," the "gold standard" of cell lines. Jonas Salk developed his polio vaccine with them. Henrietta Lacks, who in death saved countless lives, is buried nearby.

DEPARTMENT OF HISTORIC RESOURCES, 2010

HeLa Cells

- Henrietta Lacks = He La
- Cells take from Henrietta's cervical cancer at the time of her surgery
- First human cells grown in a lab that were naturally "immortal"
- These cells have never stopped dividing and reproducing since 1951
- Oldest and most commonly used human cell line in labs all over the world

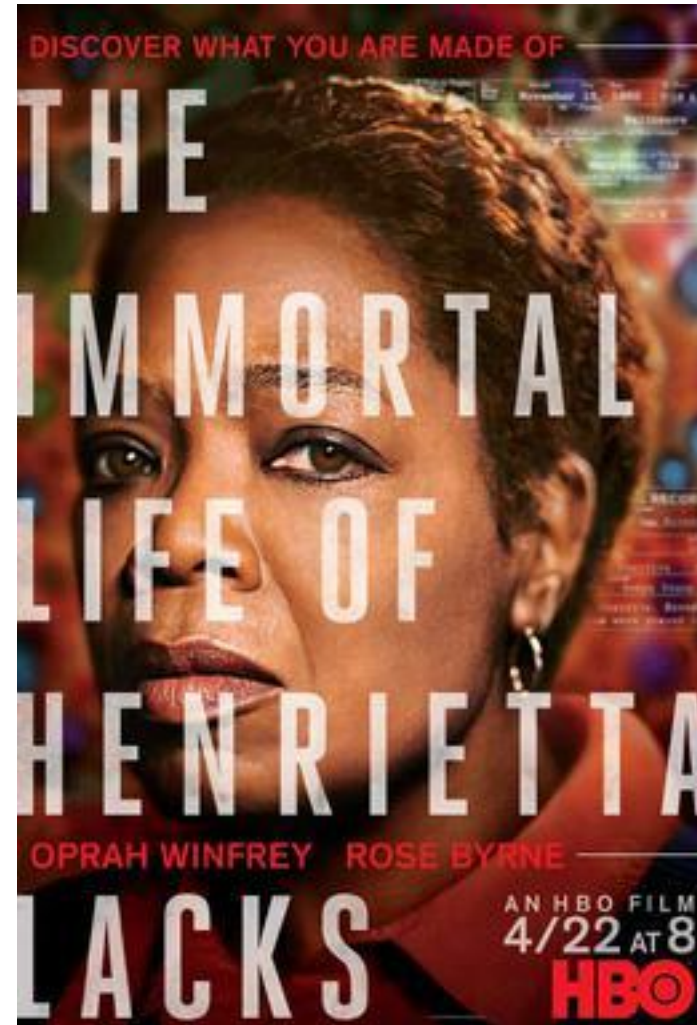


Reported in 2010

- Scientists have grown an estimated 20 tons of HeLa cells
- > 60,000 scientific articles using HeLa cells and
estimated 300 papers each month
- Almost 11,000 patents involving HeLa cells
- HeLa cell lines are known to replace other cell cultures and have contaminated millions of dollars worth of biological research

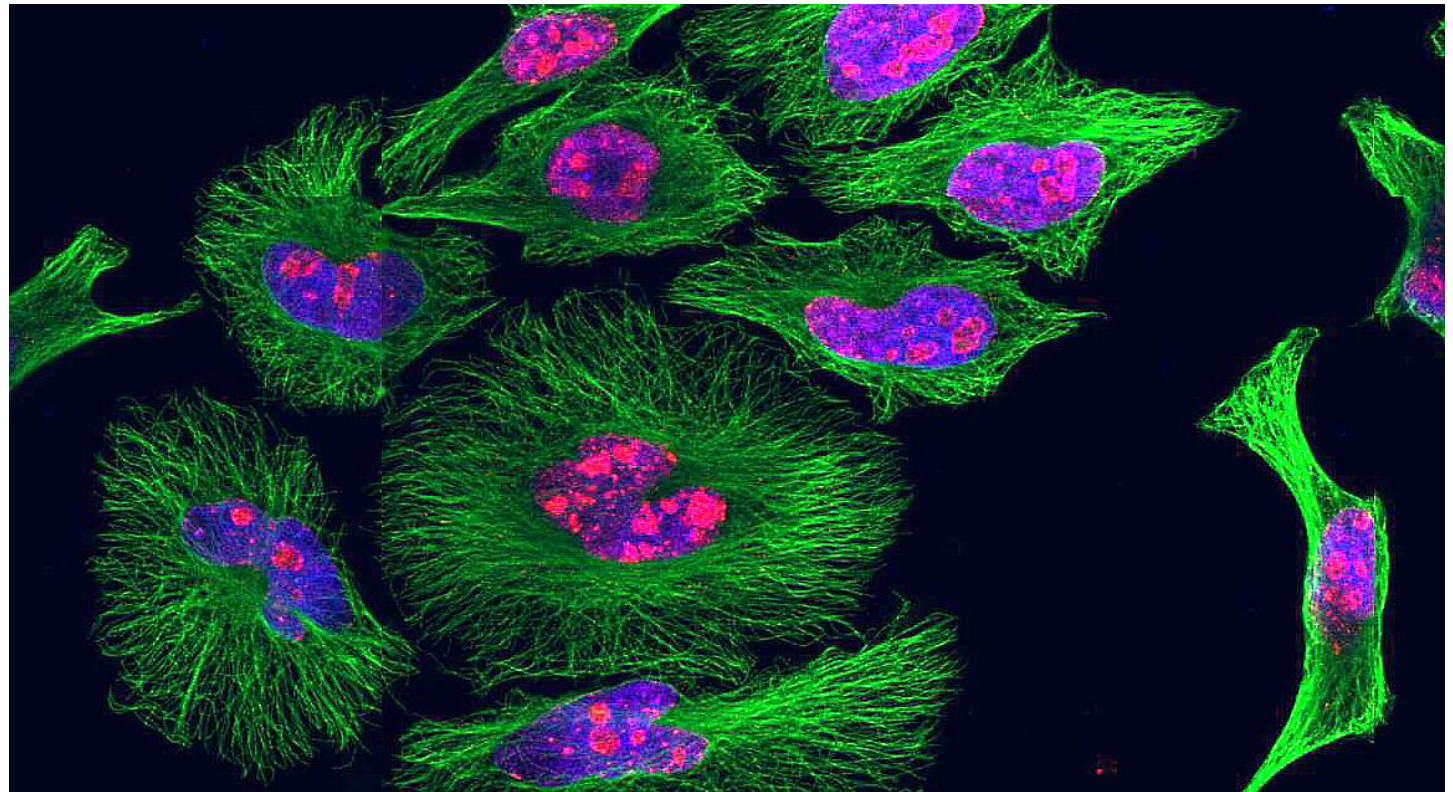
April 2017 on HBO

Oprah Winfrey in HBO's
'Immortal Life of Henrietta
Lacks'



Why can a cell line infected with a papilloma virus become “immortal”

What are papilloma viruses and where did they come from???



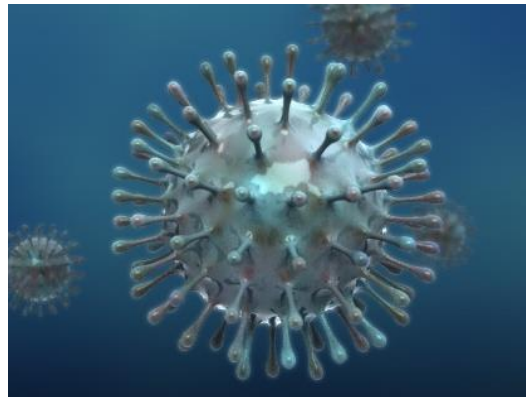
By GerryShaw <https://commons.wikimedia.org/w/index.php?curid=55821167>

Papilloma Viruses

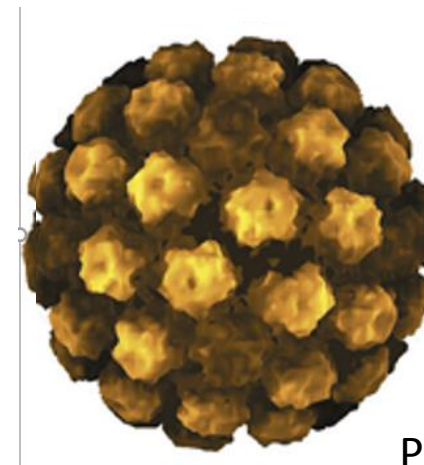
Papilloma – a warty or finger like growth



Virus – infectious agent that reproduces inside the cells of hosts. Host cells are forced to produce thousands of identical copies of the original virus



Flu virus



Papilloma virus



Papilloma Viruses (PV)

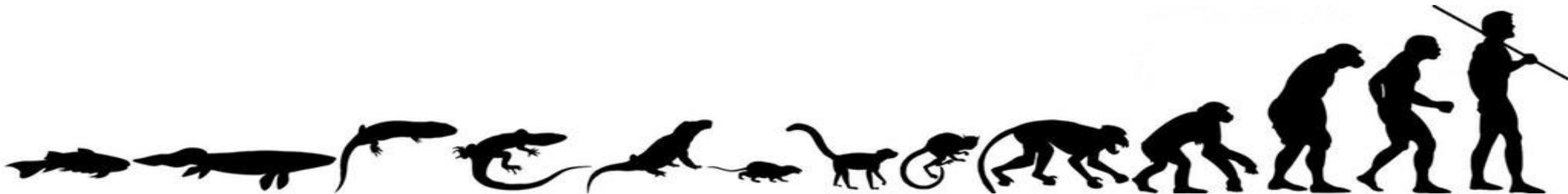
- *Large family of DNA viruses that infect the outer skin and mucosal skin (mouth, throat, anus and vagina)
- *Often cause their host no symptoms, or warty growths of the skin, some are capable of causing cancer
- *Each type of PV affect only a particular species and only particular skin areas – like hands or feet, genitals or mouth.
- *300 types of papillomaviruses have been identified, including over 200 human papillomaviruses (HPV)

Nagayasu Egawa, Viruses. 2015 Jul; 7(7): 3863–3890.

A long long long time ago

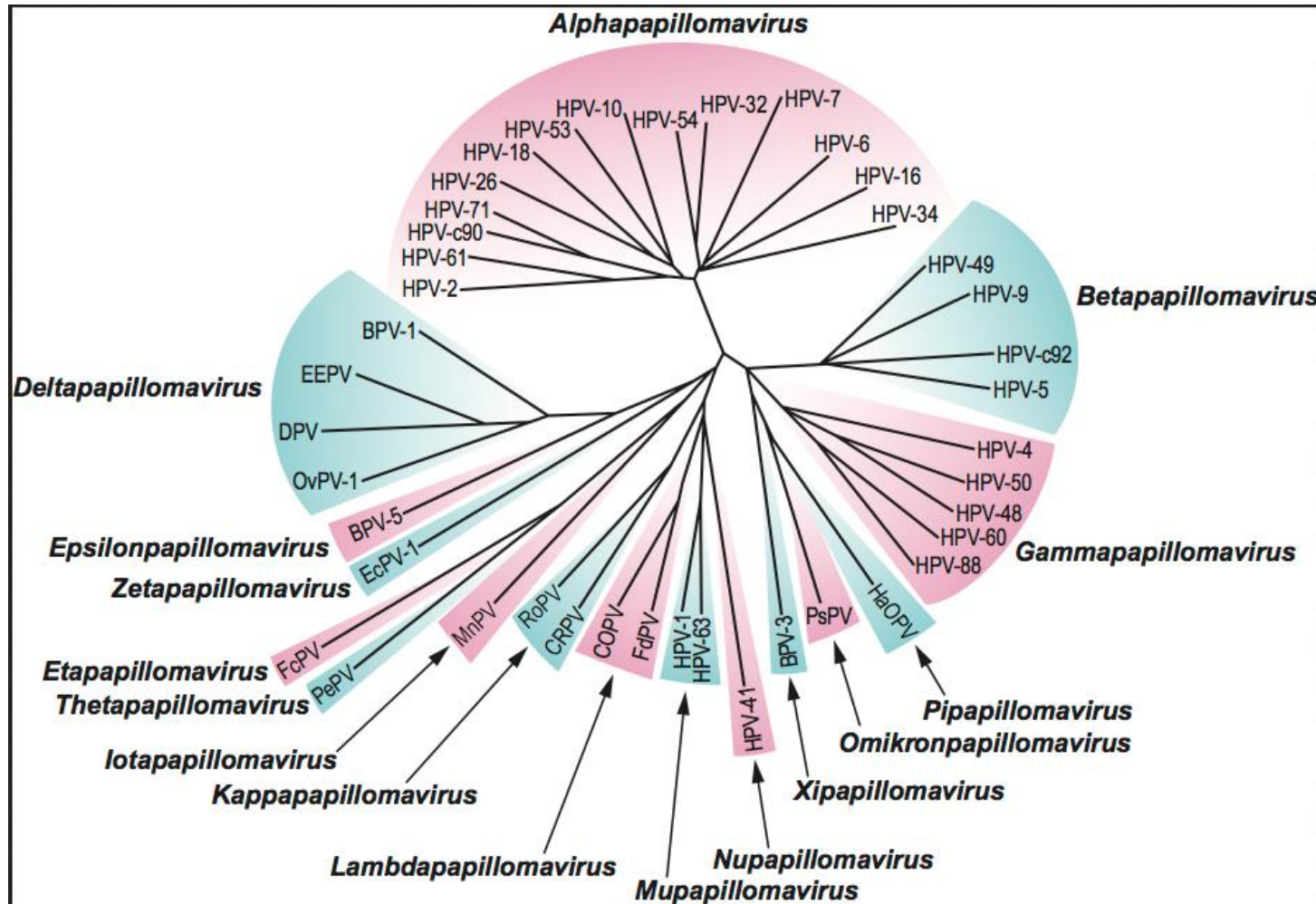
Over 400 million years ago - our fish relatives (Actinopterygii) hosted a papillomavirus. Papillomaviruses have been co-evolving with their hosts (mammals, birds and reptiles) ever since.

Human Papillomaviruses (HPV) were present in the first humans as they came into their modern form.



International Committee on Taxonomy of Viruses (ICTV)

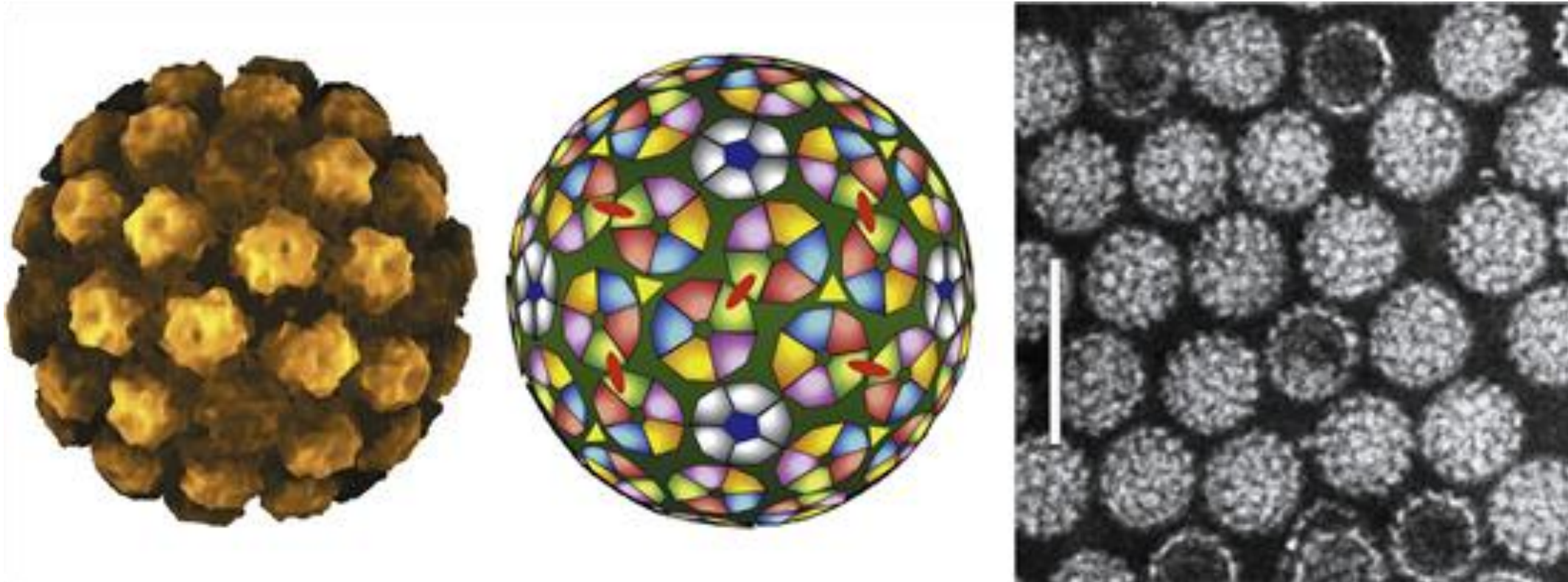
Papilloma viruses



The tree was constructed using the Tree view program (R. Page, University of Glasgow)' <http://ictv.global/report>



Papilloma Viruses



from Modis et al. (2002). EMBO J., 21, 4754–4762
<http://ictv.global/report>



*Most papillomaviruses isolated from mammals

*Five bird and three reptile species also have papillomavirus

*Therefore thought that the papillomavirus family may have emerged at the time of divergence of mammals and birds/reptiles, around 330 million years ago

*Recently, papillomavirus was detected in fish, pushing back the date of appearance of this virus family by up to 400 million years, at the time ray-finned fishes appeared



Cow Papillomas and Canine Papillomas

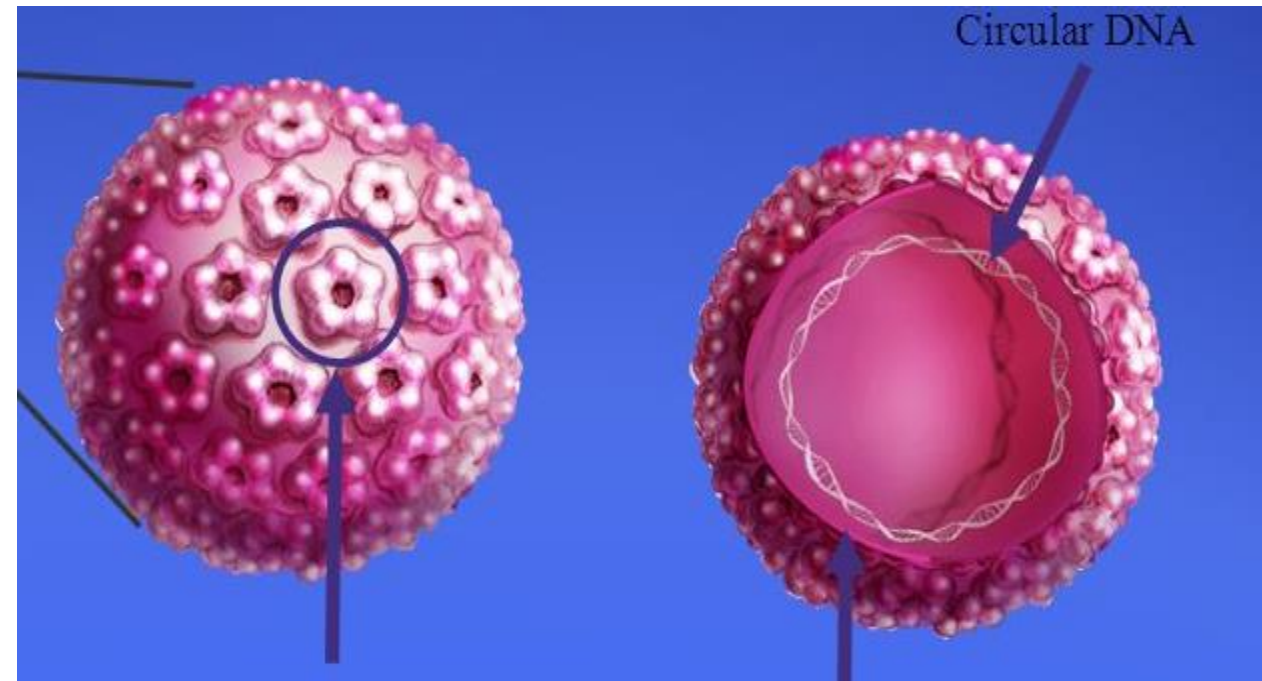


Human Papilloma Virus (HPV)

Protein capsid (shell) with a double-stranded circular DNA genome

Over 200 different HPVs identified

- 40 known to infect the genital tract
- **15 are considered high risk or "oncogenic" (able to cause cancer)**



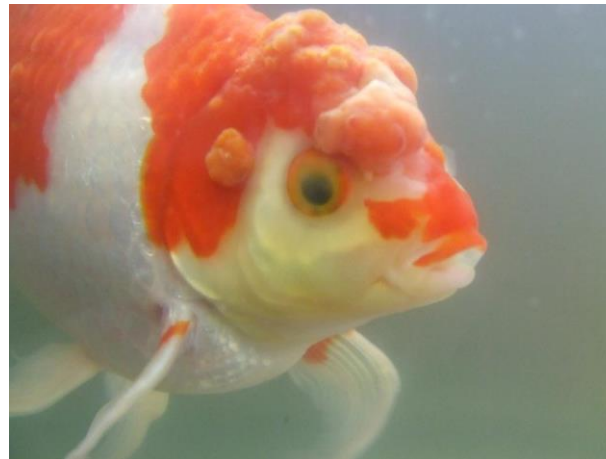
Shah KV and Howley PM, *Fields Virology 3rd edition*. 1996; 2077-106
De Villiers EM, *Papillomavirus Rep* 2001;12:57-63
[Nagayasu Egawa](#), *Viruses*. 2015 Jul; 7(7): 3863–3890.

HPV as an evolutionary marker

*HPV evolution has been very slow with little change (while fish to man evolution is quite dramatic)

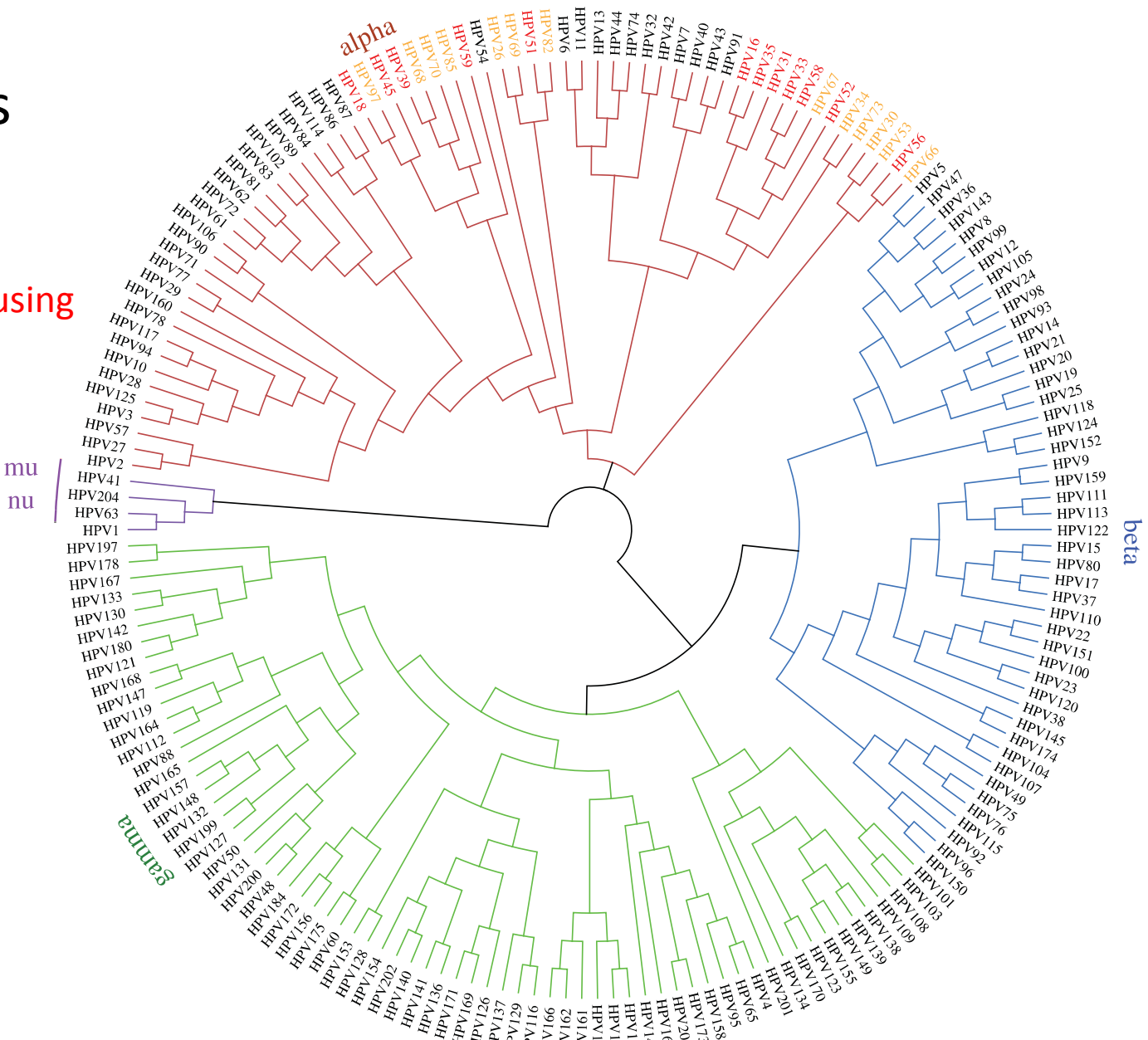
*Variants within single HPV type have been evolving for over 200,000 years

* Genetic drift of HPVs follow patterns of migration of ancient human populations

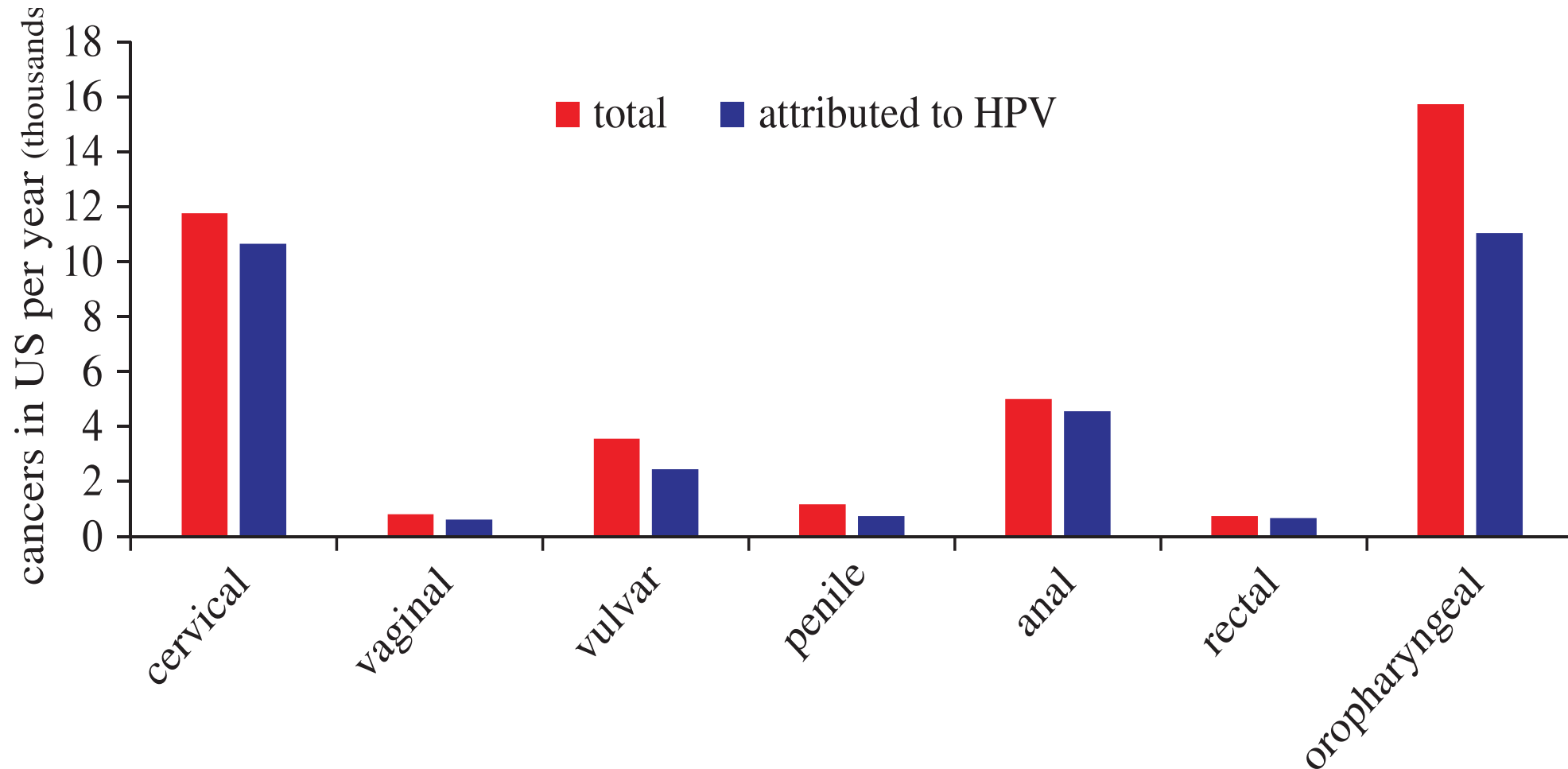


Different HPV types

Red HPV types are cancer-causing



Cancers in humans known to be caused by HPV



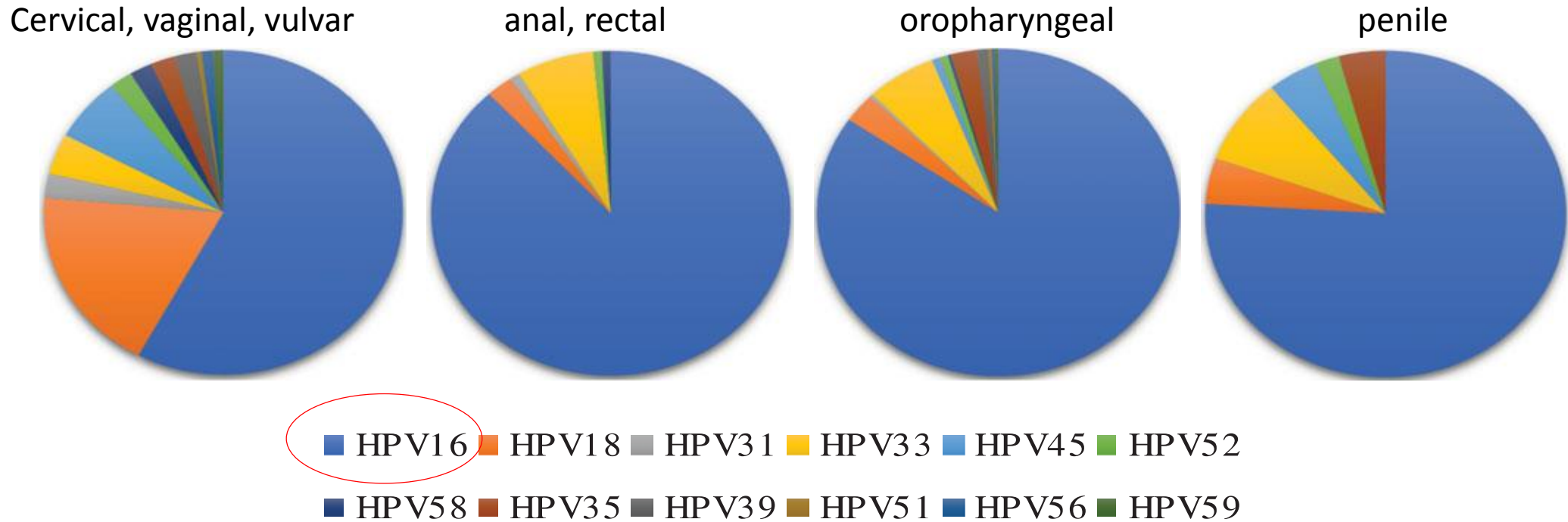
HPV in the national lime light. Celebrity, oral sex, HPV and throat cancer.



“Michael Douglas: cancer-free 7 years after treatment for HPV-16 associated throat cancer! Know about this actor’s throat cancer, its cause, and how he acquired it!”

Posted by MarriedBioraphy on September 23, 2017 | In [Health](#), [Relationship](#)

HPV type 16 causes majority of human HPV cancers



Numbers of cancers caused by HPV in the U.S.

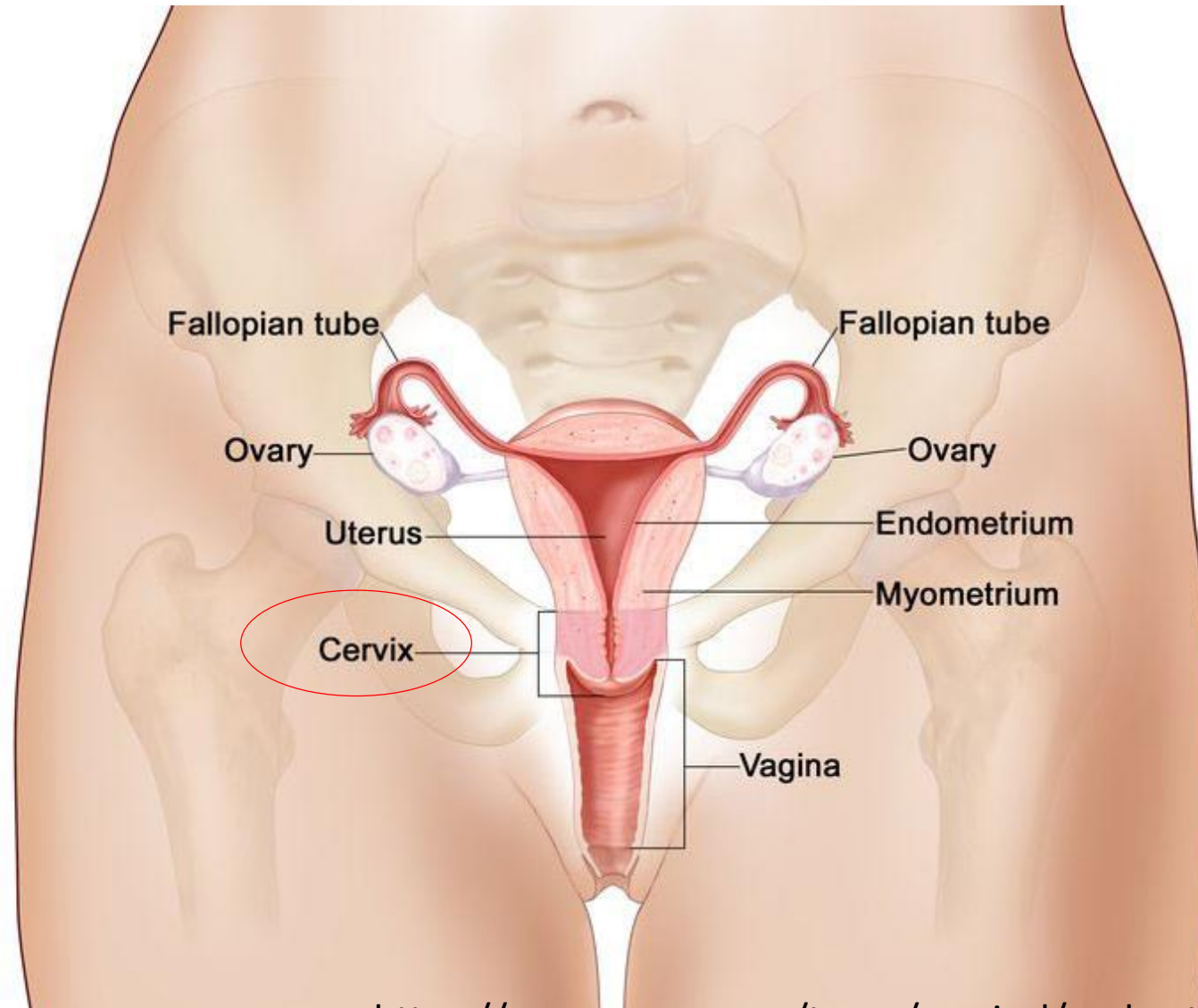
Cancer site	Average number of cancers per year probably caused by HPV†	
	Male	Female
Anus	1,400	2,600
Cervix	0	10,400
Oropharynx	7,200	1,800
Penis	700	0
Vagina	0	600
Vulva	0	2,200
TOTAL	9,300	17,600



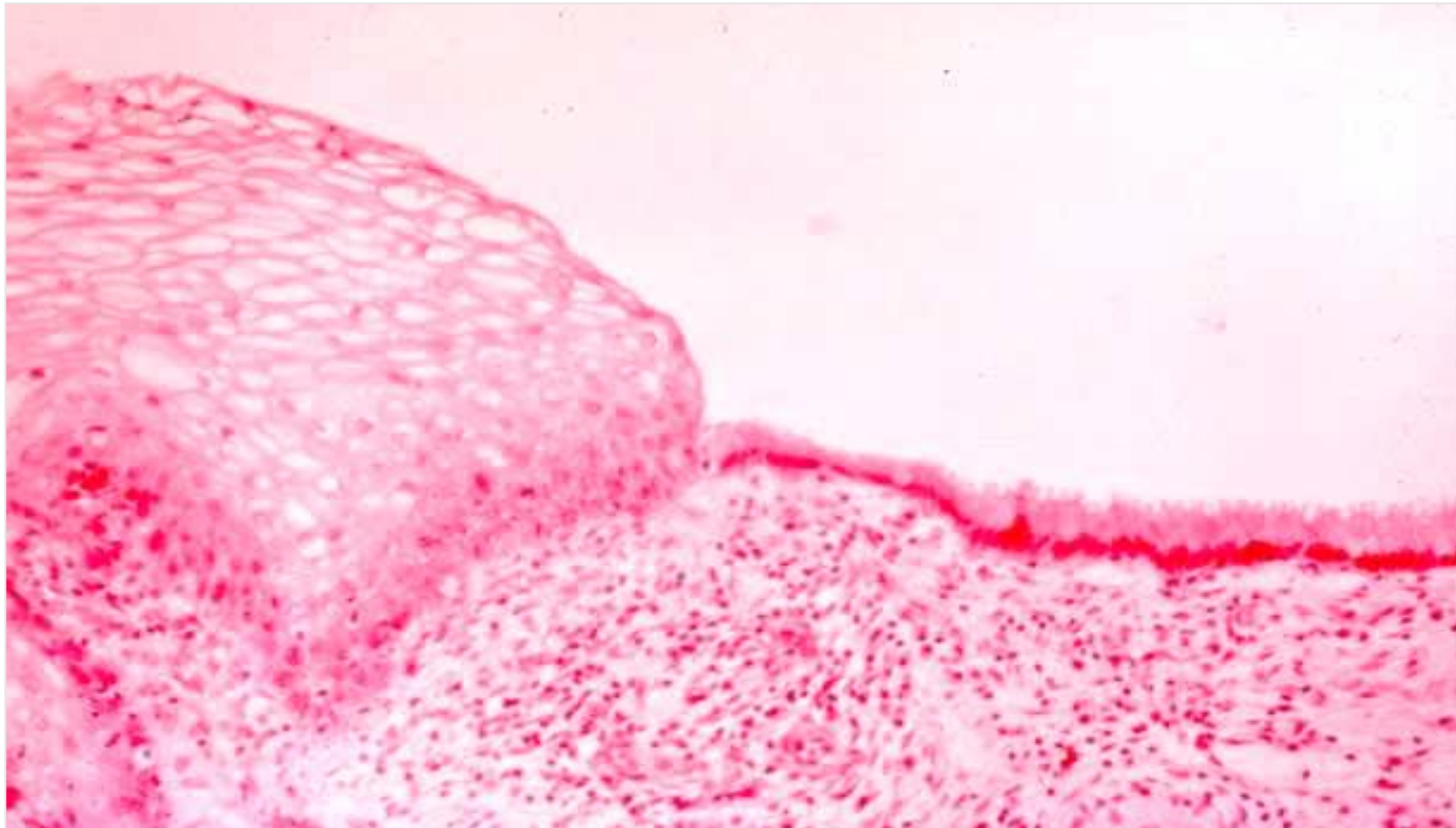
HPV, pre-cancer and cancer of the Cervix

- 1956 cervical skin cells that developed from human papilloma virus (HPV) lesions were reported. The authors called these cells koilocytotic atypia or koilocytosis, meaning “hollow”, from the Greek word koilos.
- 1983 Harald Zur Hausen – reports HPV as cause of cervical cancer

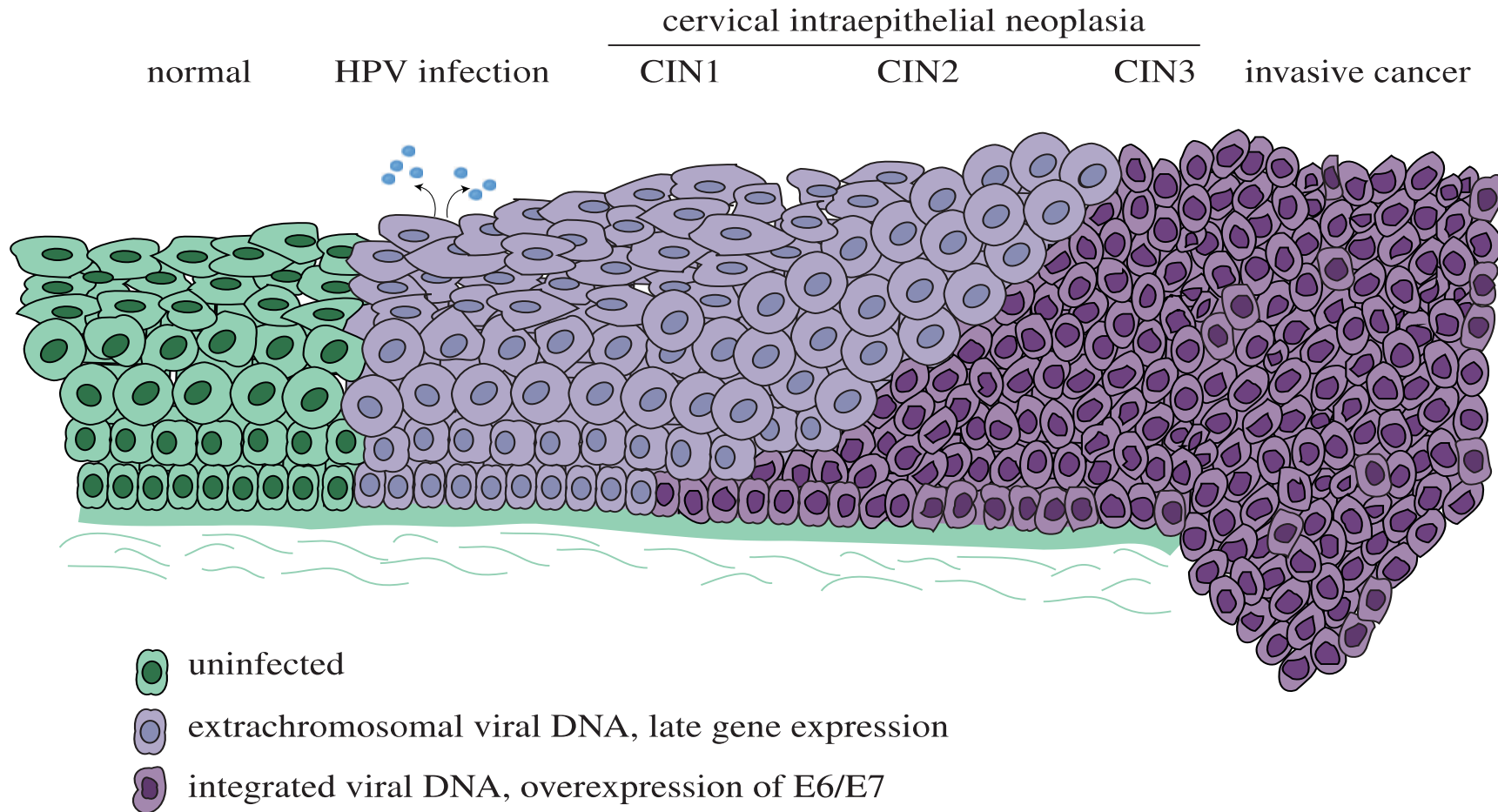
Female reproductive anatomy



Biopsy of normal tissue from the cervix...



HPV effects on skin



Pap smear showing koilocytic changes

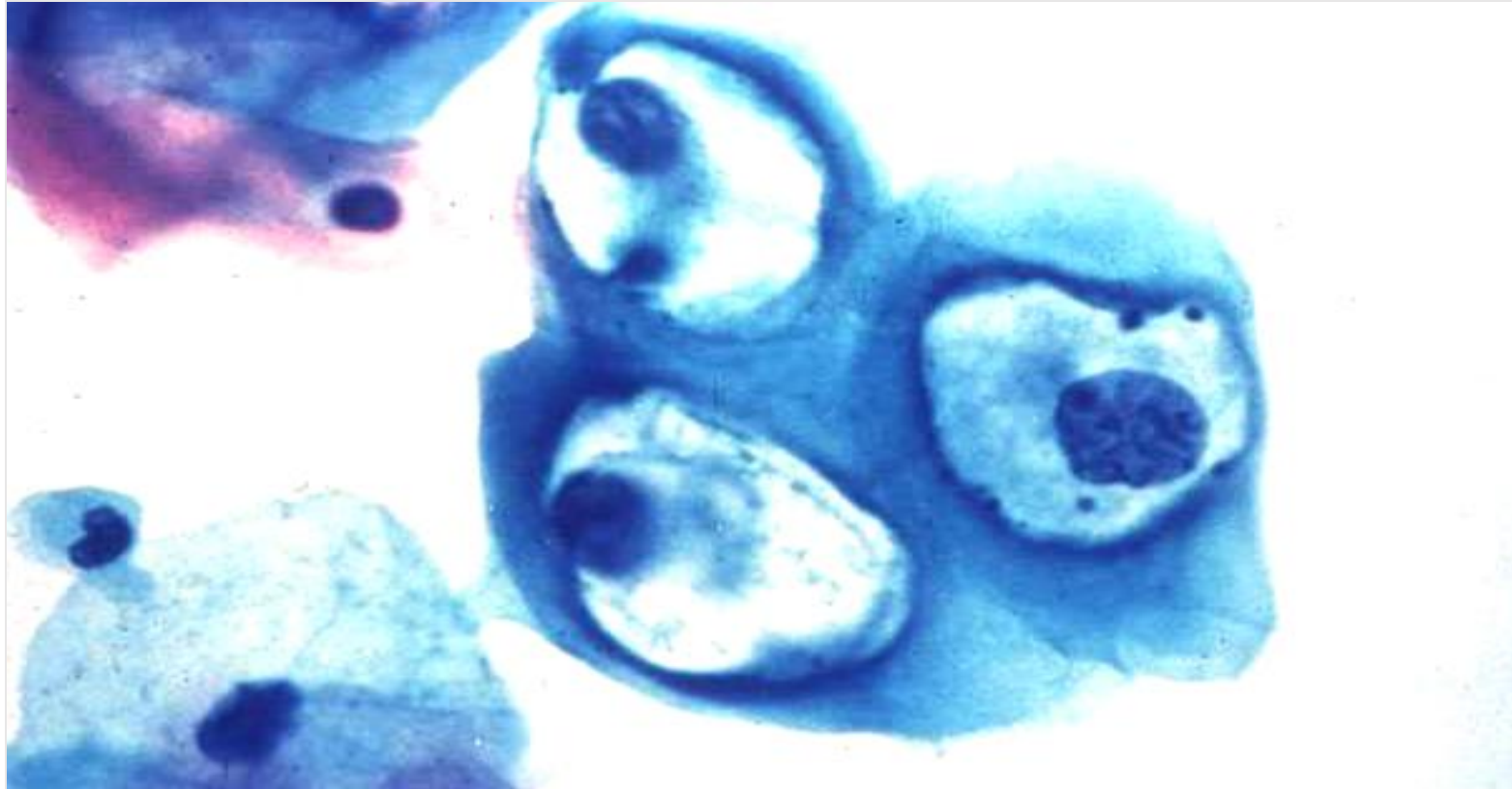
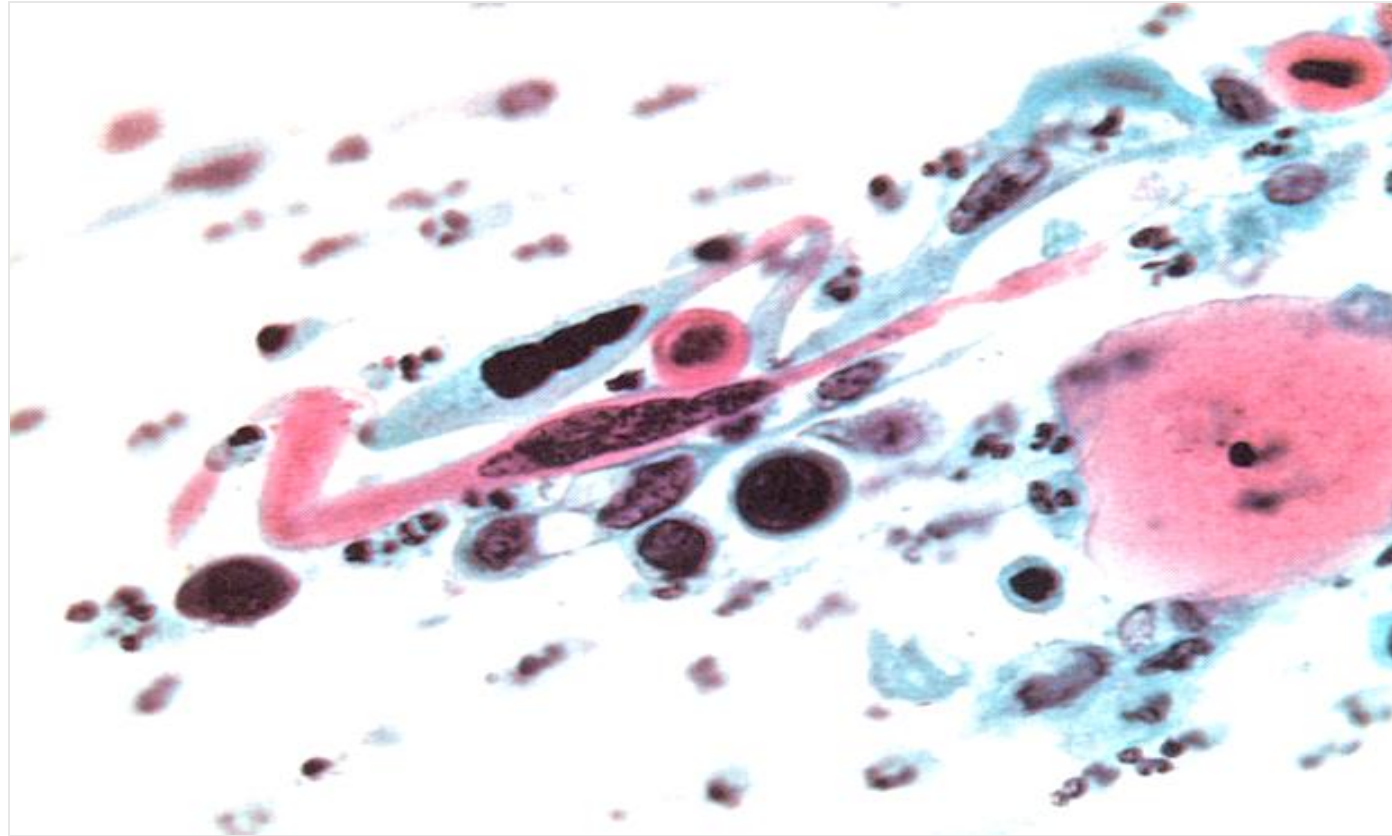
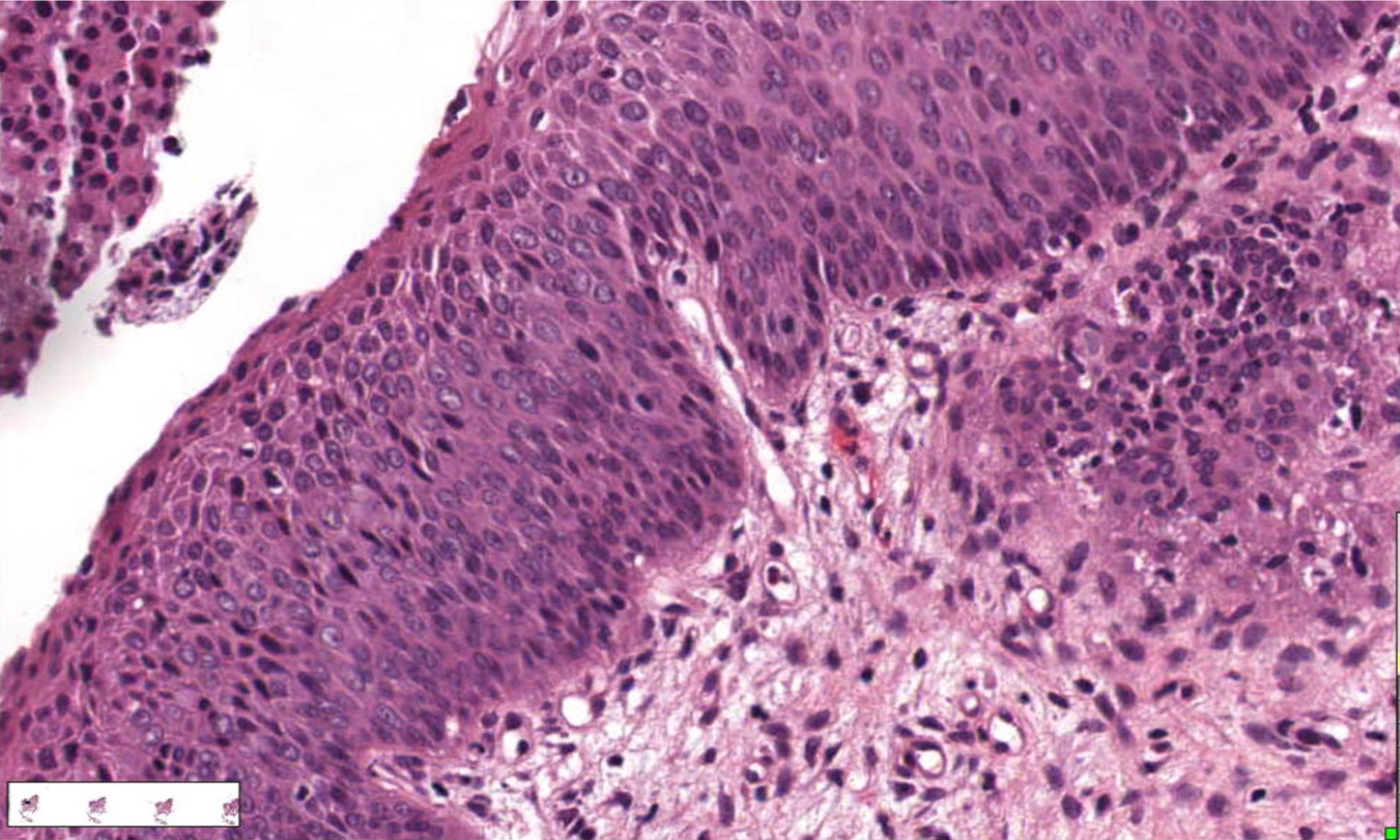


Photo - American Society of Clinical Pathologists

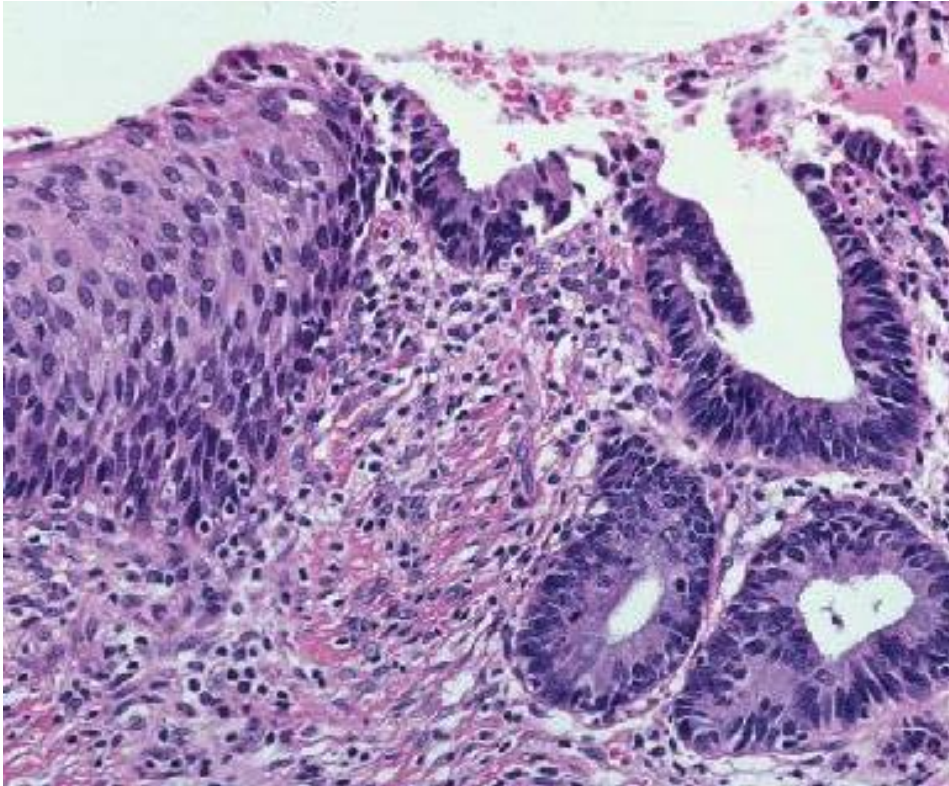
Pap smear showing cancer



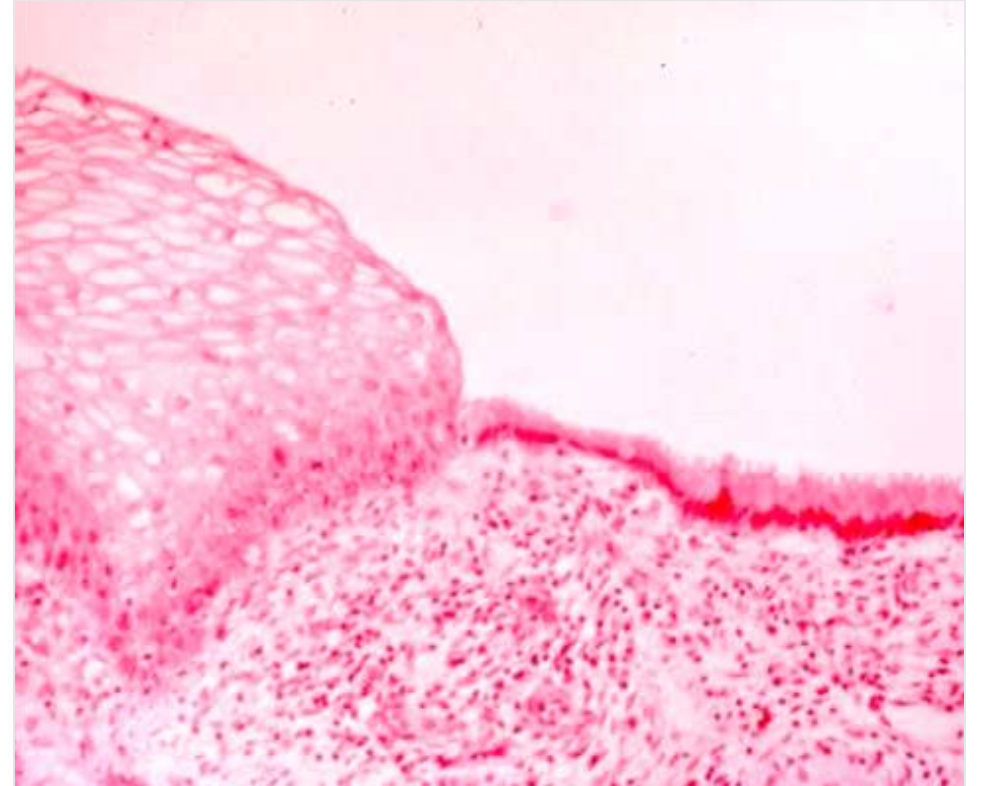
Biopsy shows high grade dysplasia.



Pre cancer skin biopsy



Normal skin biopsy



How does HPV cause cancer?

1. Immune Evasion

HPV infects self-renewing cells at the bottom of skin cell layers

*ensures long-term viral persistence

Viral particles only produced at the top layers of skin

*helps the virus escape detection by the immune system.



How does HPV cause cancer?

2. Turn off cancer protection in cells and make cells immortal

High risk HPVs can insert their DNA into human DNA and this leads to high production of certain viral proteins which affect the cell's safeguards against cancer

Key functions of the HPV cancer genes (E6 and E7) are:

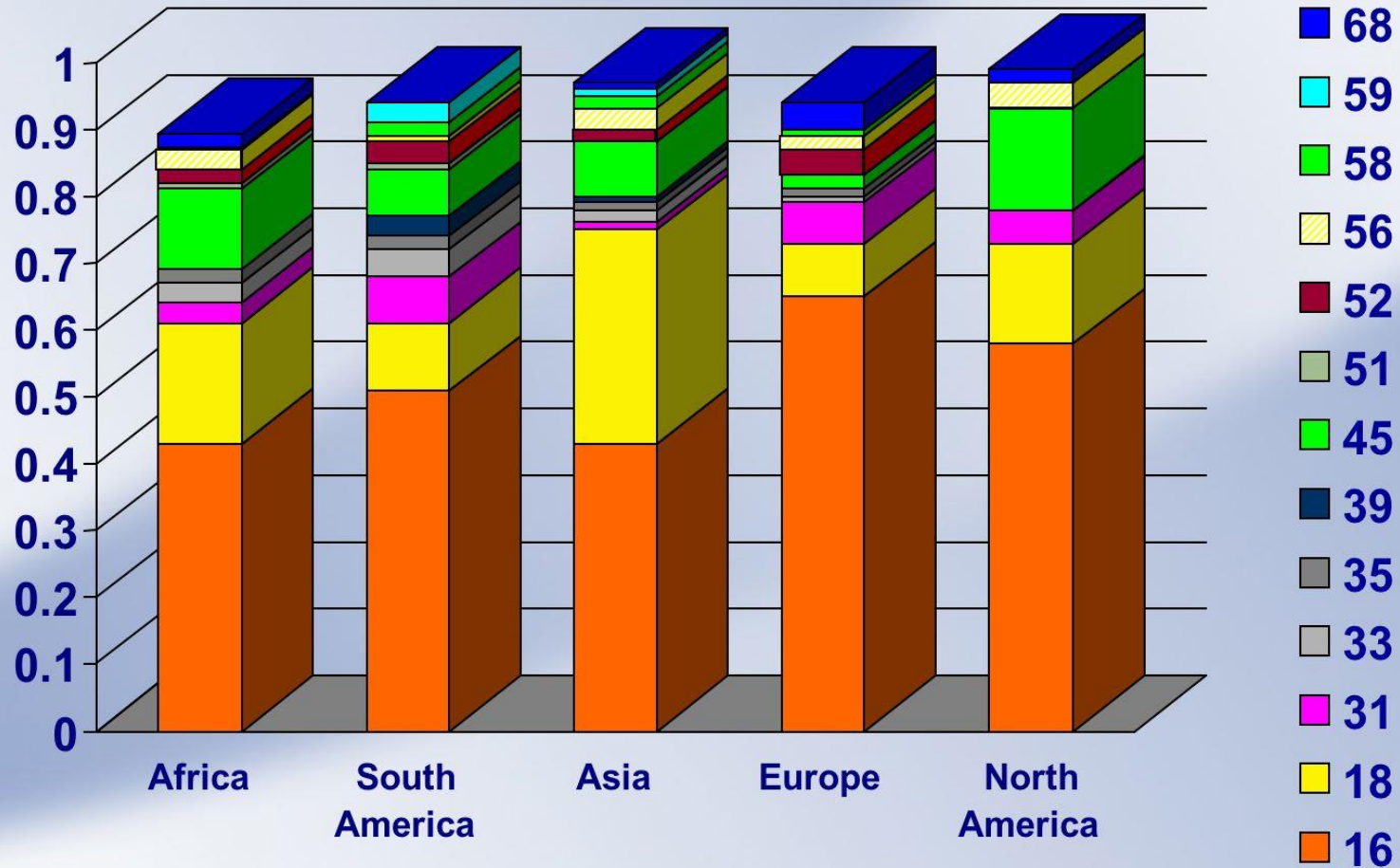
- *destruction of normal tumor suppressor proteins that safe-guard against cancer by initiating cell death when the cell is not functioning normally

- *increase in telomerase which allows a cell line to divide without ever reaching a limit. This unbounded growth is a feature of cancer



HPV Types in Cervical Cancer by Region

15 types are associated with cervical cancer



Most genital HPV exposures result in brief infections and not cervical cancer!

- * Cancer causing HPVs are sexually transmitted
- * about 30% of young women become infected within 24 months of their first sexual exposure
- * Infection can result in mild cervical abnormalities but about 90% will clear within 2 years
- * Long-term persistent infection puts individuals at high risk for precancerous skin changes (cervical intraepithelial neoplasia)

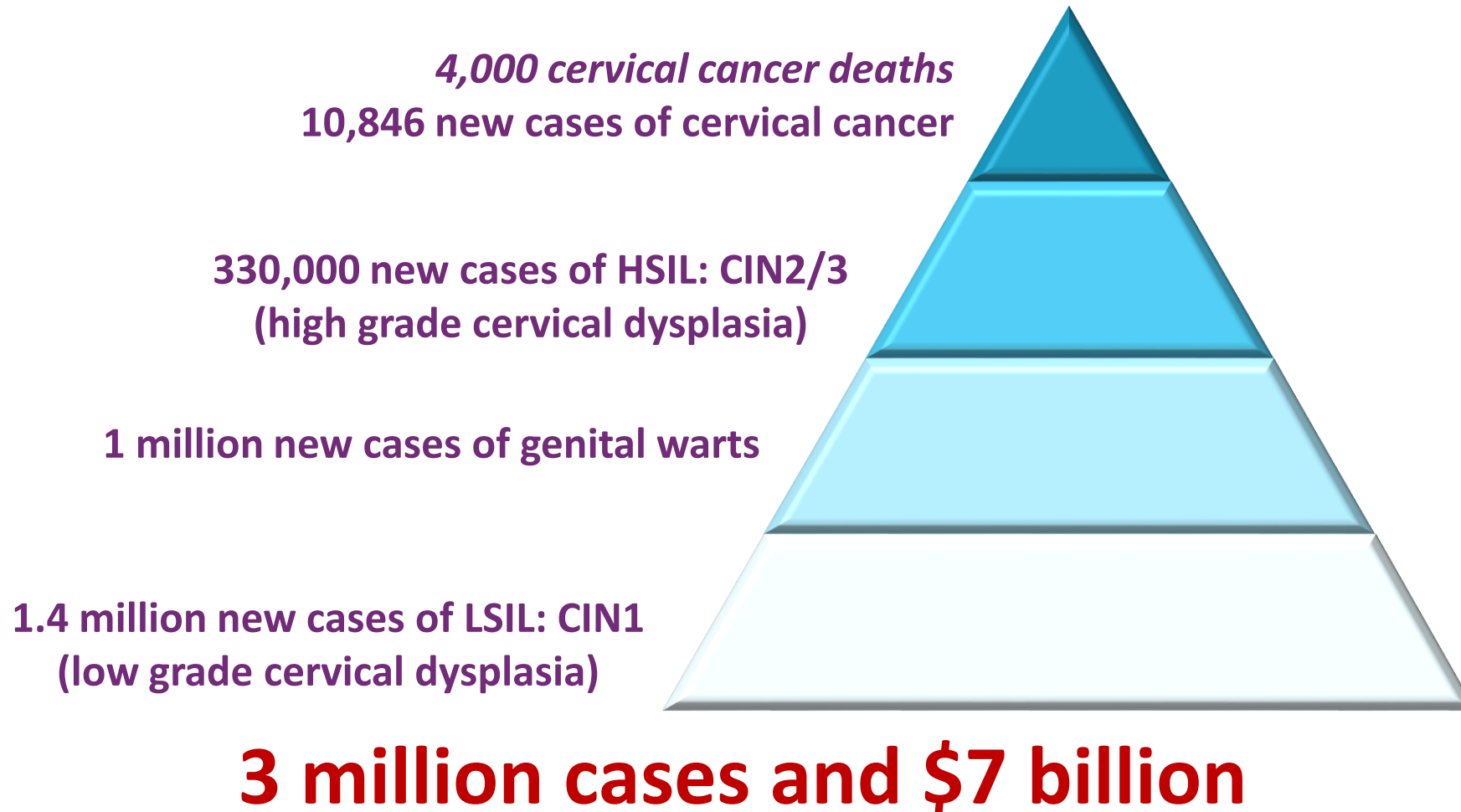
HPV infection

- Most women and men will be infected with at least one type of genital HPV at some point in their lives
 - Estimated 79 million Americans currently infected
 - 14 million new infections/year in the US
 - HPV infection is most common in people in their teens and early 20s
- Most people will never know that they have been infected

Jemal A et al. J Natl Cancer Inst 2013;105:175-201

- Estimated that 75% (3 out of every 4) people in the US will have been exposed to HPV by age 49

2. Annual burden of genital HPV-related disease in U.S. females:



Are you
ready for
the future?

HPV vaccine arrives for prime time 2005-06

Wall Street Journal

Forbes

The New Yorker

CNN

The Nation

NEJM

BMJ

Lancet

OB GYN Journals

Wall Street Journal 5/20/2005

Merck “will have to navigate tricky waters” to get recommendations for routine HPV vaccination among young people and may face “political concerns that the vaccine reduces health risks of sex for young people.”



The New Yorker March 13, 2006

“This (HPV vaccine) is a cancer vaccine and an immensely effective one. We should be proud and excited. It has the potential to save hundreds of thousands of lives each year.”

- David Baltimore
 - Nobel laureate, President of California Institute of Technology

The New Yorker March 13, 2006

“Premarital sex is dangerous, even deadly. Let’s not encourage it by vaccinating ten-year-olds so they think they’re safe.”

- Senator Tom Coburn, MD of Oklahoma
 - Family Physician

Scientific challenges preceded societal/political challenges. Barriers to a HPV vaccine:

Each HPV type has unique surface molecules

No single anti-HPV possible which would protect against many HPV types

Cross immunity thought to be unlikely

Need vaccine against many types = polyvalent

Lowry DR, Schiller JT, Monogr NATL Cancer Inst 1998;23:27-30

1st FDA approved vaccine 2006 – against HPV 16, 18, 6 and 11

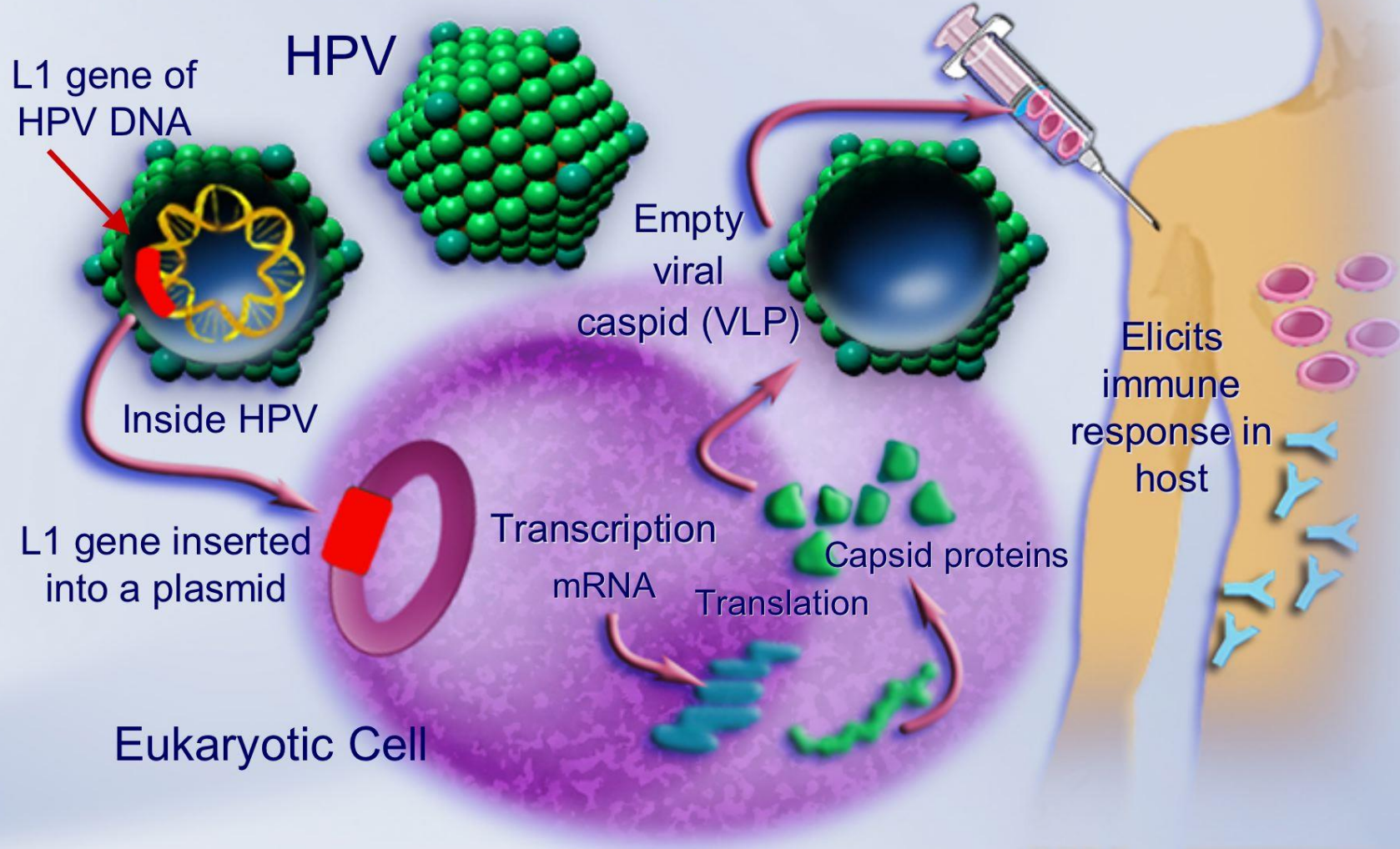
2/2014 FDA approved Gardasil 9 against – additional HPV types 31, 33, 45, 52, 58



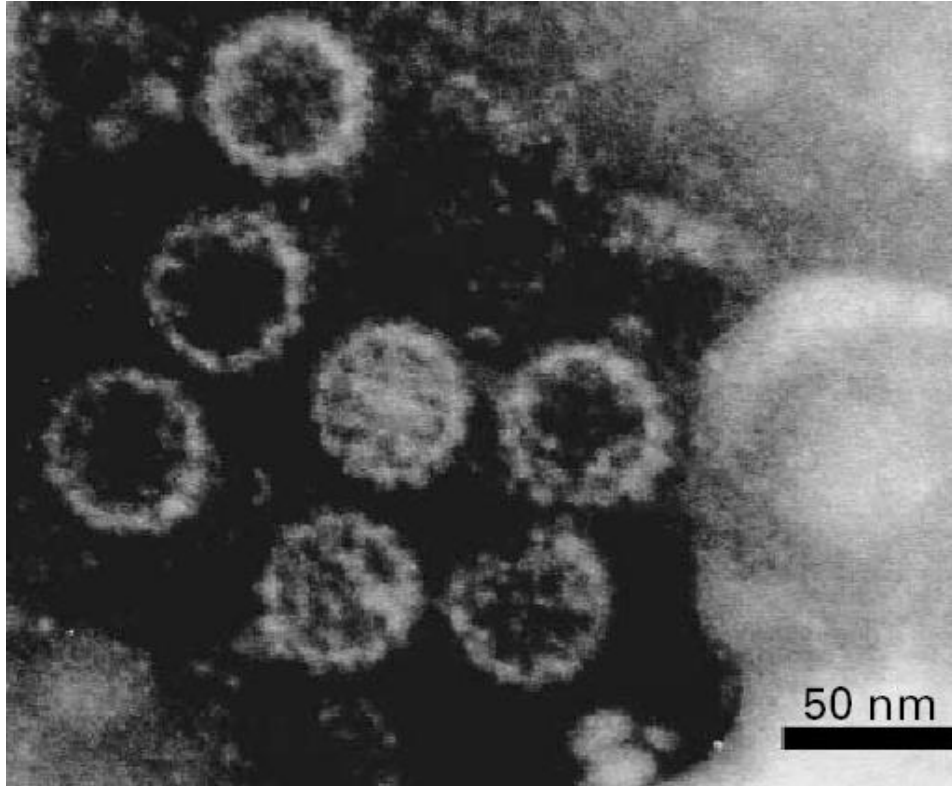
Papillomavirus-like particle (VLP) vaccines

- *Basically empty cargo vessels that the immune system can not distinguish from real virus – like a car with no engine
- *Cause production of neutralizing antibodies

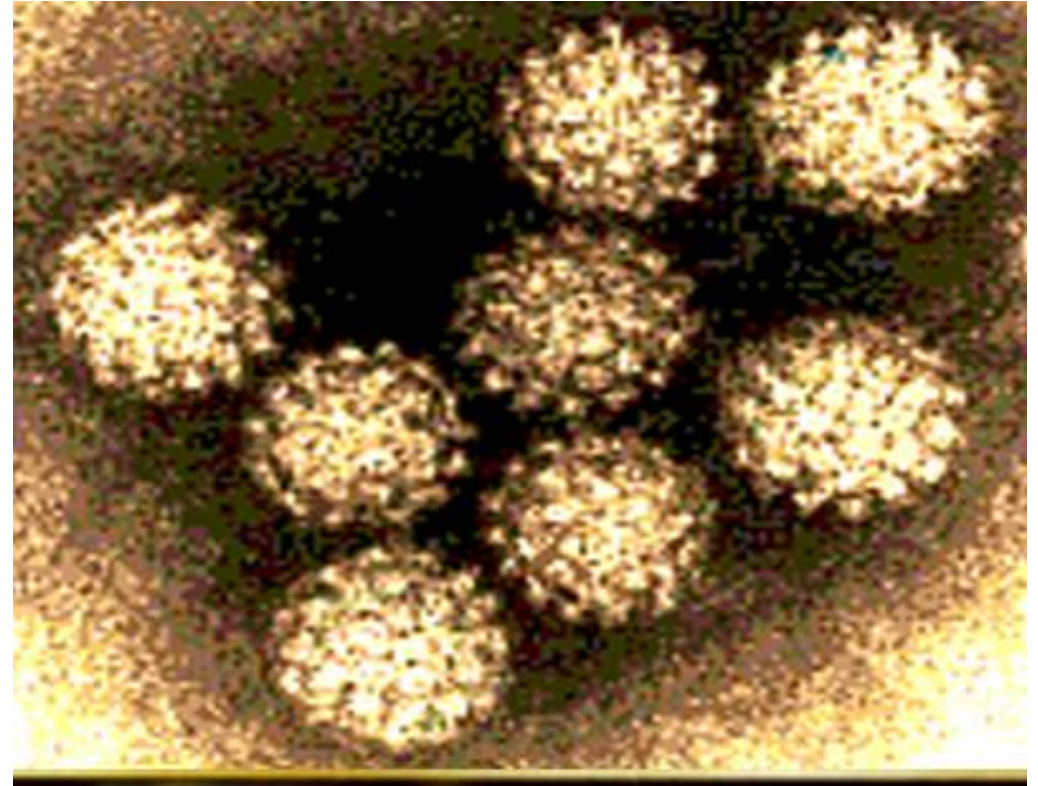
HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis



HPV VLP vs HPV virus



Crum C, N Engl J Med 2002;347:1703-5



Advisory Committee on Immunization Practices (ACIP) HPV vaccine recommendation:

- Routine vaccination at age 11 or 12 years*
- Vaccination recommended through **age 26 for females** and through **age 21 for males** not previously vaccinated
- Vaccination recommended for men **through age 26** who have sex with men (MSM) or are immunocompromised (including persons HIV-infected)

*vaccination series can be started at 9 years of age
MMWR 2015;64:300-4

The Nation, May 30, 2005

“Giving HPV vaccine to young women could be potentially harmful, because they may see it as a license to engage in premarital sex.”

- Bridget Maher of the Family Research Council

“Raise your hand if you think that what is keeping girls virgins now is the threat of getting cervical cancer when they are 60 from a disease they’ve probably never heard of.”

- Katha Pollitt, The Nation, May 30,2005



So...is the HPV vaccine safe and effective???



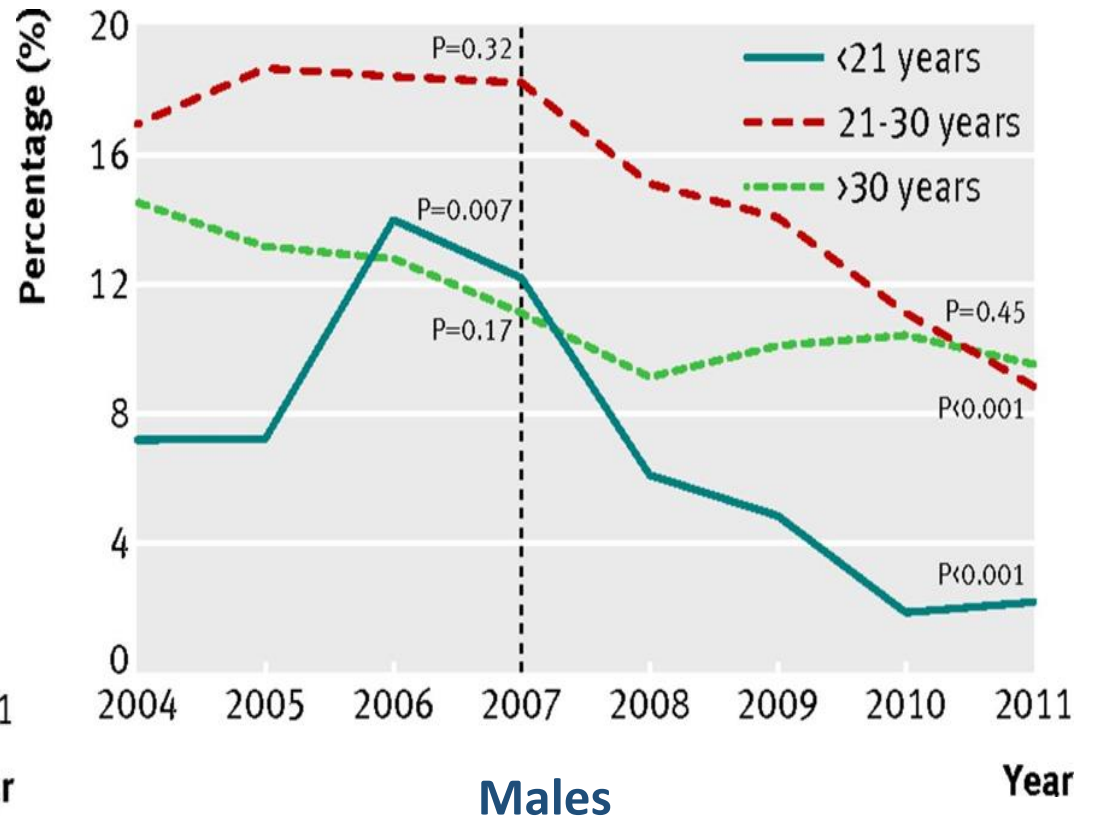
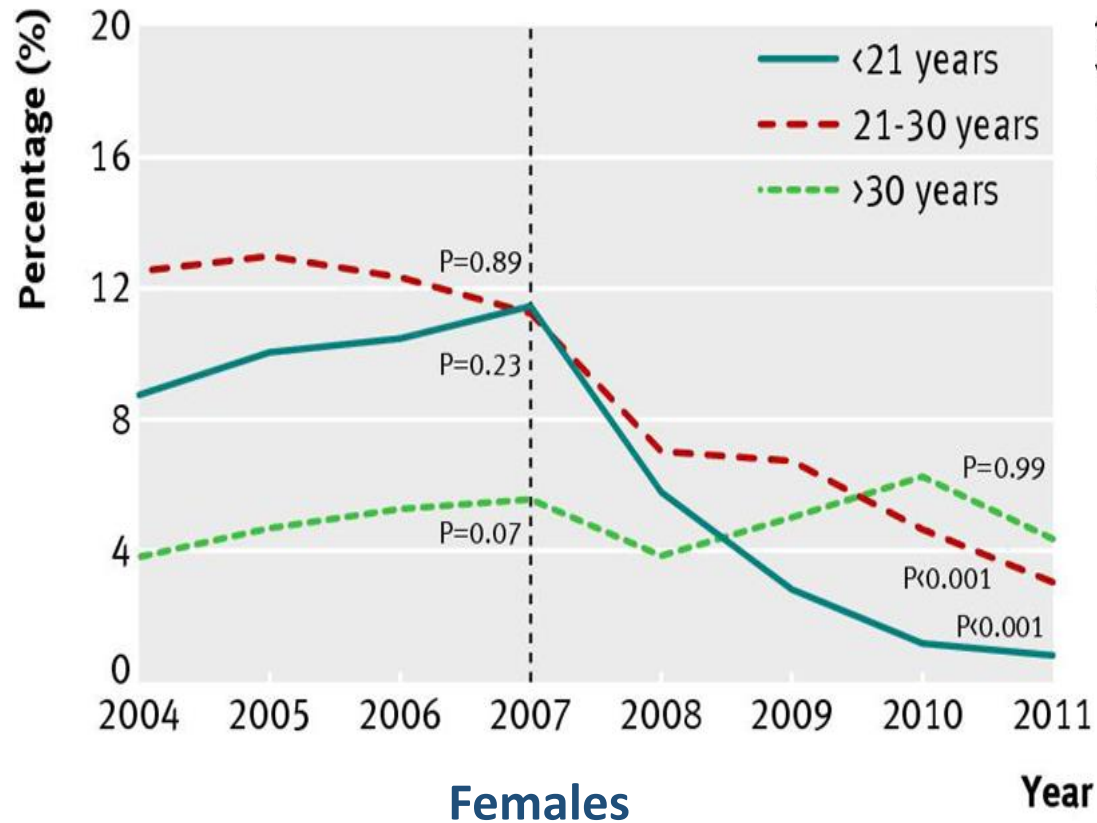
Systematic review and meta-analysis: population-level impact of HPV vaccination

- Review of 20 studies in 9 high income countries
- In countries with *>50% coverage*, among 13-19 year olds
 - HPV 16/18 prevalence decreased at least 68%
 - Anogenital warts decreased by ~61%
- Evidence of herd effects
- Some evidence of cross protection against other types

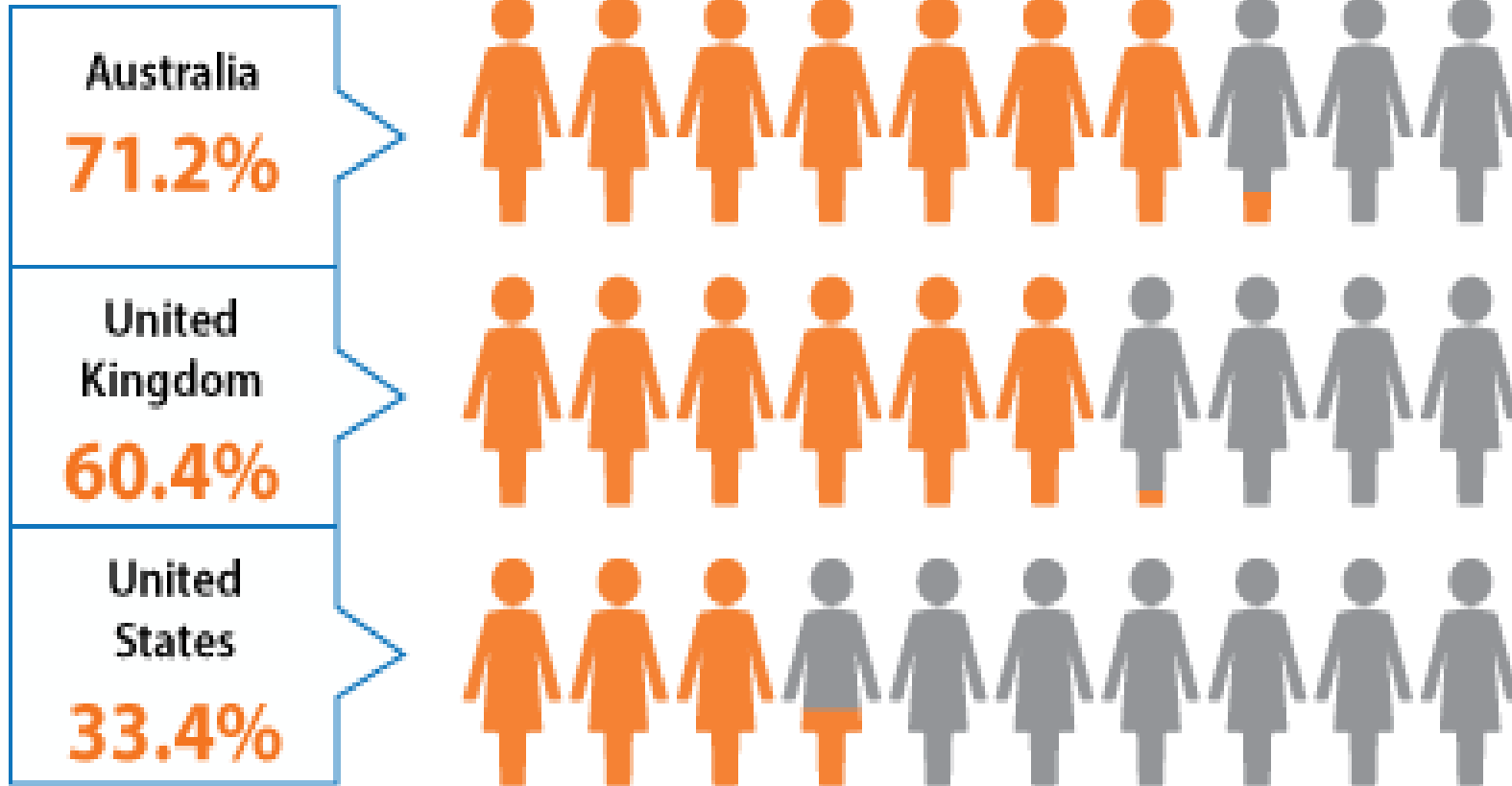
Drolet et al. Lancet Infect Dis 2015

Impact of HPV vaccination in Australia

Proportion of Australian born females and males diagnosed as having genital warts at first visit, by age group, 2004-11

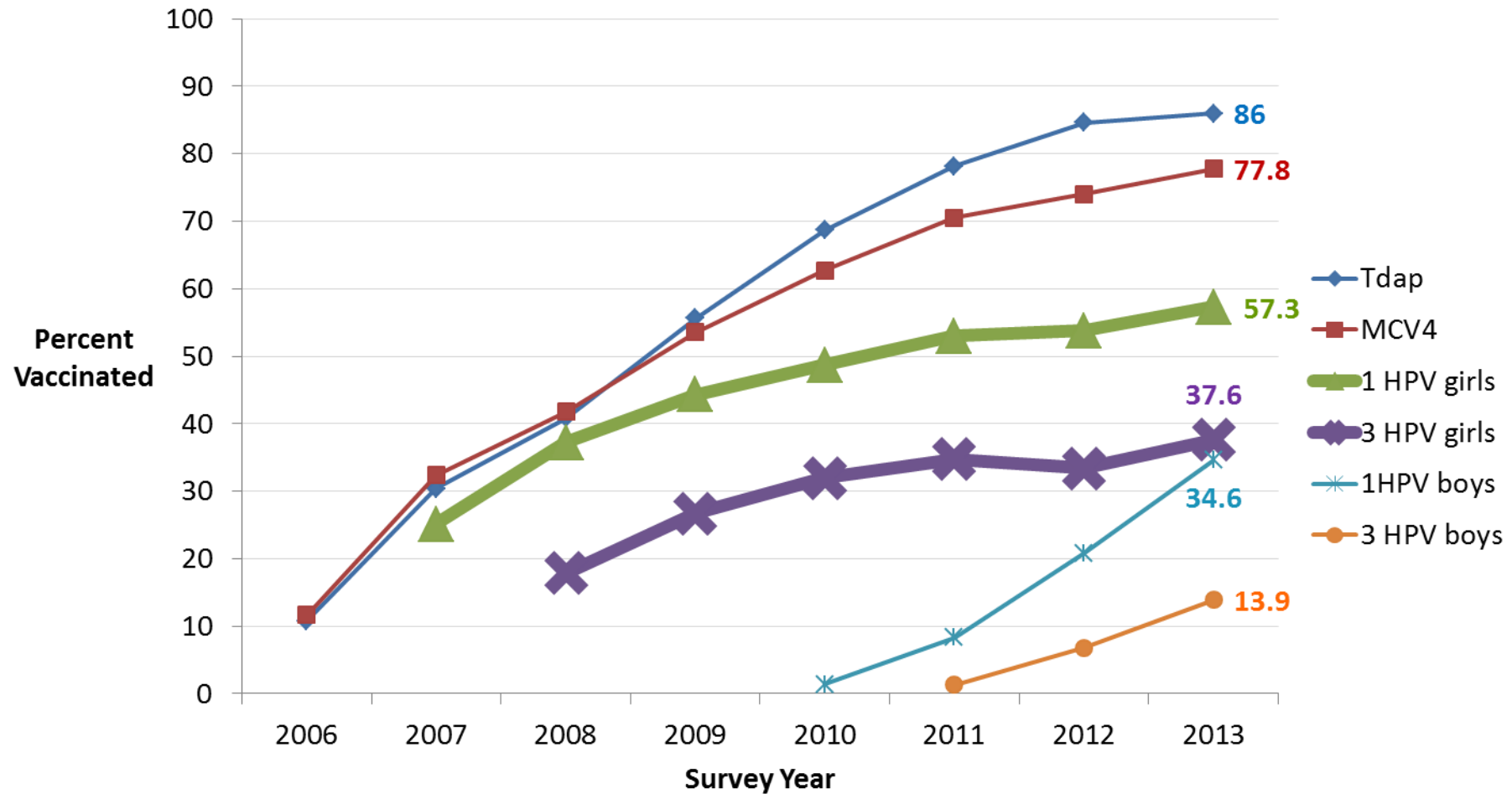


HPV Vaccine Three-Dose Coverage



Among Girls in High-Income Countries

Adolescent vaccination coverage United States, 2006-2013



Abstinence

Abstinence supporters argue that eliminating the threat of infection would only encourage teenagers to have sex. HPV is not prevented by condoms

“I personally object to vaccinating children when they do not need vaccinations, particularly against a disease that is one hundred percent preventable with proper sexual behavior.”

- Leslee J. Unruh
 - Founder and president of the Abstinence Clearinghouse



Abstinence

Abstinence has little evidence of preventing premarital sex, but does reduce contraception use and sexually transmitted infection prevention when a person intending virginity has sex.

“One thing that I have learned is that belief doesn’t change reality.”

- C. Everett Koop MD



5. An Overview of quadrivalent HPV vaccine safety – 2006 to 2015

- *HPV vaccine is currently approved in 133 countries and over 178 million doses were distributed globally as of December 2014
- *There have been 15 studies totaling > one million pre-adolescents, adolescents, and adults from various countries
- *Only fainting, and possibly skin reactions were associated with vaccination
- *Serious adverse events were extensively studied, and no increase in the incidence of these events was found compared with background rates.

Pediatr Infect Dis J. 2015 Jun 22 (Epub ahead of print)

HPV vaccine continues to work 10 years after vaccination

*10 years post vaccination HPV-16/18 vaccine shows continued efficacy against pre-cancer, irrespective of HPV type.

*Studies also showed wide cross-protection against other high risk HPV types 31/33/45 in the long-term



Why the controversy over a simple, safe and highly effective cancer prevention vaccine?

“It all comes down to the evils of sex. That’s an ideological position impervious to empirical evidence.”

- James Trussell, director of the Office of Population Research at Princeton.



Human Papilloma Virus

*An Ancient virus that has so cleverly evolved that it resulted in a cell line that grows exponentially and lives forever.

*Science at its best and worst.

*A cancer vaccine that is highly effective, yet maligned and grossly underused (in the US). If we had a vaccine that could eliminate breast, colon or prostate cancer – would there be any controversy?



A happy healthy cervix! Questions?

