

# Anal Cancer and HPV

by

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# objectives

- <http://www.youtube.com/watch?v=QI1go72c5H8>

# Conflict of Interests

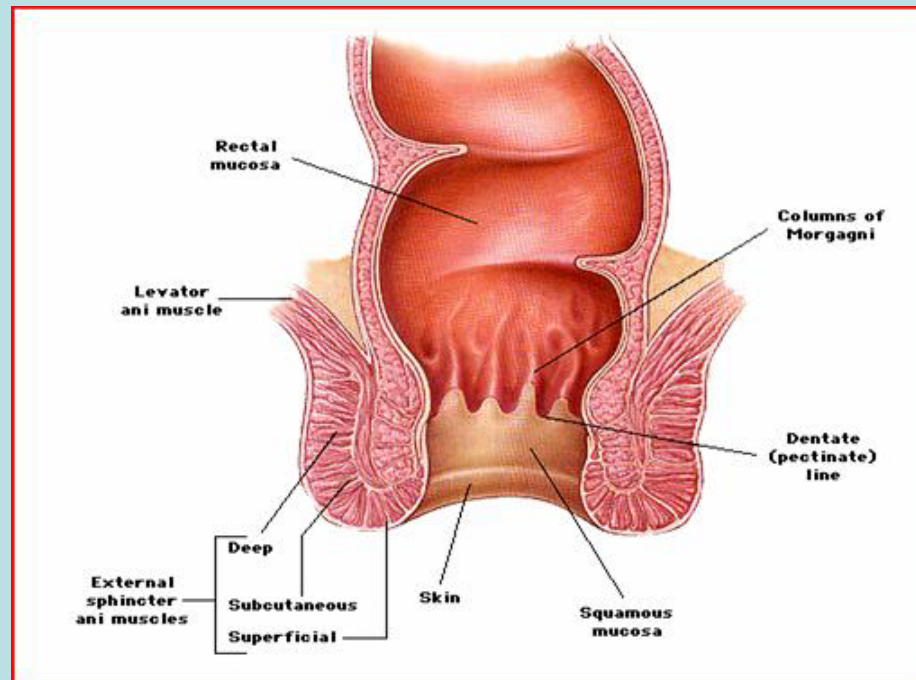
# Acknowledgements !!

- Dr John Hay – BCCA
- Up-to-Date
- Wikipedia
- Google

# The Anus



# THE ANUS part 2



**Anatomy of the anus** The anus consists of a mucosa-lined anal canal and an epidermis-lined anal margin. The proximal end of the anal canal begins anatomically at the junction of the puborectalis portion of the levator ani muscle and the external anal sphincter, and extends distally to the anal verge, a distance of approximately 4 cm. The anal canal is divided by the dentate line, which overlies the transition from glandular (columnar) to squamous mucosa that is often referred to as the transitional zone. The anal margin begins approximately at the anal verge, which corresponds to the introitus of the anal orifice. It represents the transition from the squamous mucosa to the epidermis-lined perianal skin, and extends to the perianal skin. (Reprinted by permission from Ryan, DP, Compton, CC, Mayer, RJ, N Engl J Med 2000; 342:792.)

# Human Papilloma Virus

- **Human papillomavirus (HPV)** is a member of the papillomavirus family of viruses that is capable of infecting humans. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes.
- Human papillomaviruses (HPVs) are a group of more than 150 related viruses, of which more than 40 can be sexually transmitted.
- More than 30 to 40 types of HPV are typically transmitted through sexual contact and infect the anogenital region

# HPV

- HP Viruses are of DNA type containing 7900 base pairs.
- HPV is implicated in cancer of the anus. Using PCR, one group has identified 29 individual HPV types and 10 HPV groups from the anal canal of men who have sex with men (MSM).

# History of HPV

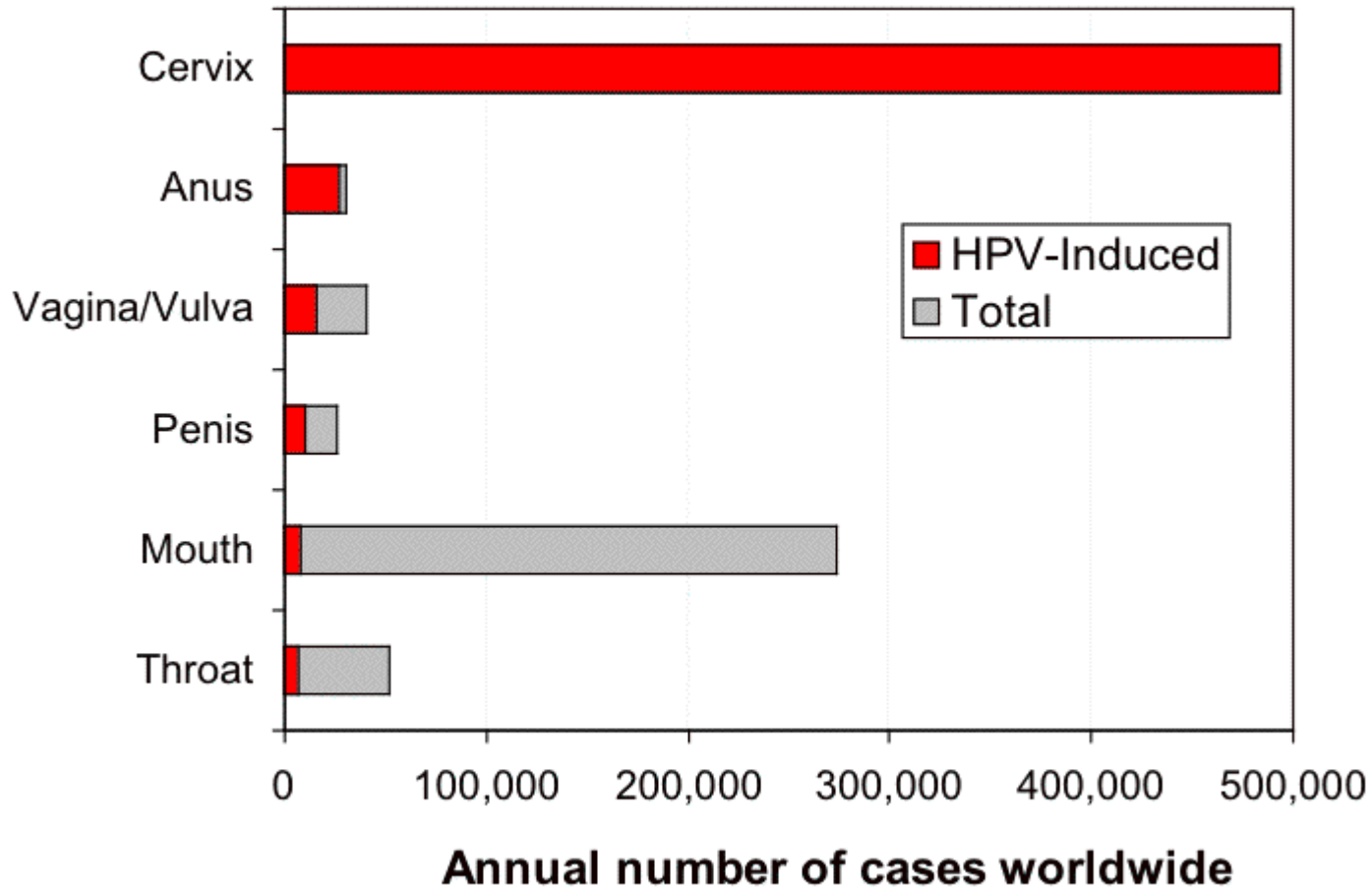
- In 1972, the association of the human papilloma viruses with [skin cancer](#) in [epidermodysplasia verruciformis](#) was proposed by [Stefania Jablonska](#) in Poland.
- In 1978, Jablonska and Gerard Orth at the [Pasteur Institute](#) discovered HPV-5 in [skin cancer](#).
- In 1976 [Harald zur Hausen](#) published the hypothesis that human papilloma virus plays an important role in the cause of [cervical cancer](#).
- In 1983 and 1984 zur Hausen and his collaborators identified HPV16 and HPV18 in [cervical cancer](#).

# Incidence

- Worldwide in 2002, an estimated 561,200 new cancer cases (5.2% of all new cancers) were attributable to HPV, making HPV one of the most important infectious cause of cancer.
- The [American Social Health Association](#) reported estimates that about 75-80% of sexually active Americans will be infected with HPV at some point in their lifetime. By the age of 50 more than 80% of American women will have contracted at least one strain of genital HPV.
- It was estimated that, in the year 2000, there were approximately 6.2 million new HPV infections among Americans aged 15–44; of these, an estimated 74% occurred to people between ages of 15 and 24.

- The spectrum of HPV types in the anal canal is similar to that described in the cervix and is associated with the same "risk" phenotypes.
- 
- HPV-16 is the most commonly detected HPV type associated with anal cancer as well as cervical cancer.

# Cancer Incidence related to HPV



- Most HPV infections in young females are temporary and have little long-term significance.
- Seventy percent of infections are gone in 1 year and ninety percent in 2 years.
- Median duration of infection=8 months
- However, when the infection persists — in 5% to 10% of infected women — there is high risk of developing precancerous lesions of the cervix, which can progress to invasive cervical cancer.

- Odds are about 50-50 that a sexually active woman will contract the virus that causes cervical cancer at some point in her life, but researchers in Hawaii have discovered that the risk of infection may be just as high in another disturbing site.
- Anal infections of HPV appear to be as common as cervical infections, according to an article published in the April issue of the Journal of Infectious Diseases

# Transmission

- HPV is released from infected desquamating cells.
- Transmission mainly via direct contact with infected cells
- Transmission of genital HPV typically occurs through sexual contact.



- The suggestion that the risk of anal HPV infection is as common the risk of cervical infection is a new one.
- It's not clear exactly how the women contracted anal HPV.
- The findings are important because anal HPV infection is strongly linked with anal cancer, a rare but increasing disease that famously afflicted 1970s superstar Farrah Fawcett in 2006.

Around 9 million viewers tuned into to Dateline NBC's special two-hour program about Farrah Fawcett's battle with cancer and saw an intimate portrait of the actress at a troubling time in her life



# A case

- Mr S is a 47 yr male who is HIV +ve for 19yrs, on anti-retroviral treatment. Has a 10yr history of condylomata, not treated because of thought that treatment worse than the problem!
- 2yrs prior to consult thought he had a swelling in skin of anus.
- 2months ago felt split in skin from anus to scrotum.
- Remains most of day in bed. Smokes marijuana for relief.

- A CT done August 2011 shows a large mass 8.7cm diameter in the anus and rectum.
- Diagnosis T3 N2 M0 squamous cell carcinoma of rectum.
- His viral load was undetectable and CD4 count was 240.



# Stunning view



# The problem

- ***This is a case of a photographer photographing another photographer. The following pictures were taken by Hans van de Vorst from the Netherlands at the Grand Canyon, Arizona . The descriptions are his own. The identity of the photographer in the photos is unknown.***

***I was simply stunned seeing this guy standing on this solitary rock in the Grand Canyon .***

***The canyon's depth is 900 meters here. The rock on the right is next to the canyon and safe.***

- ***Watching this guy wearing flip flop sandals, with a camera and a tripod I asked myself 3 questions:***

***1. How did he climb that rock?***

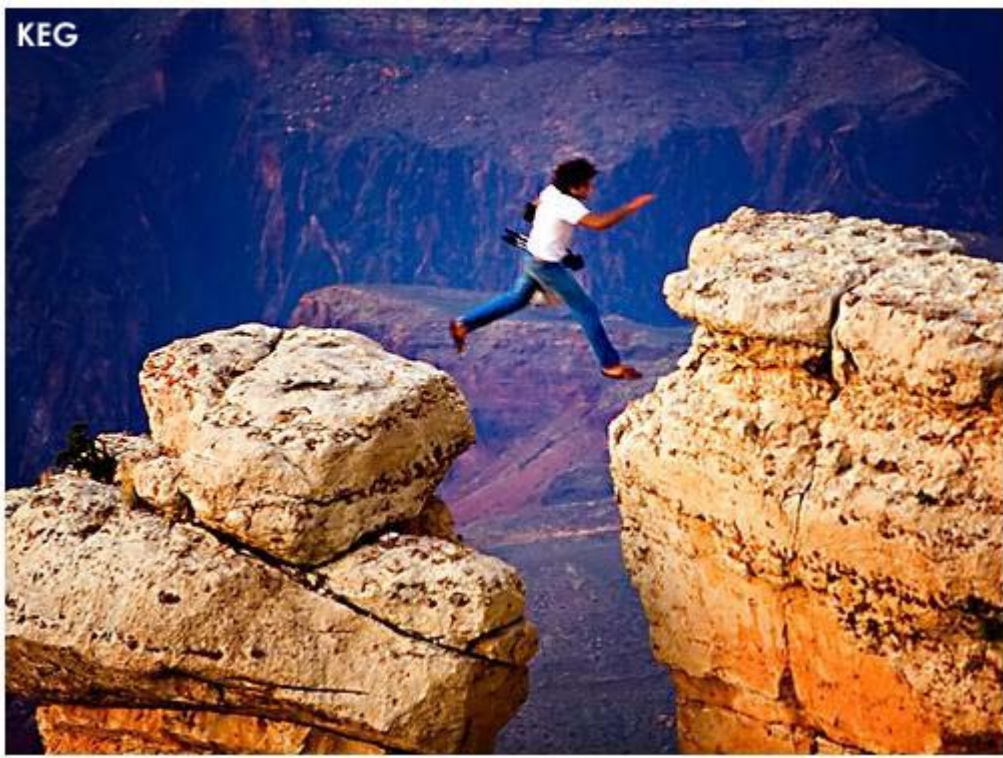
***2. Why not take that sunset picture from that rock to the right, which is perfectly safe?***

***3. How will he get back?***

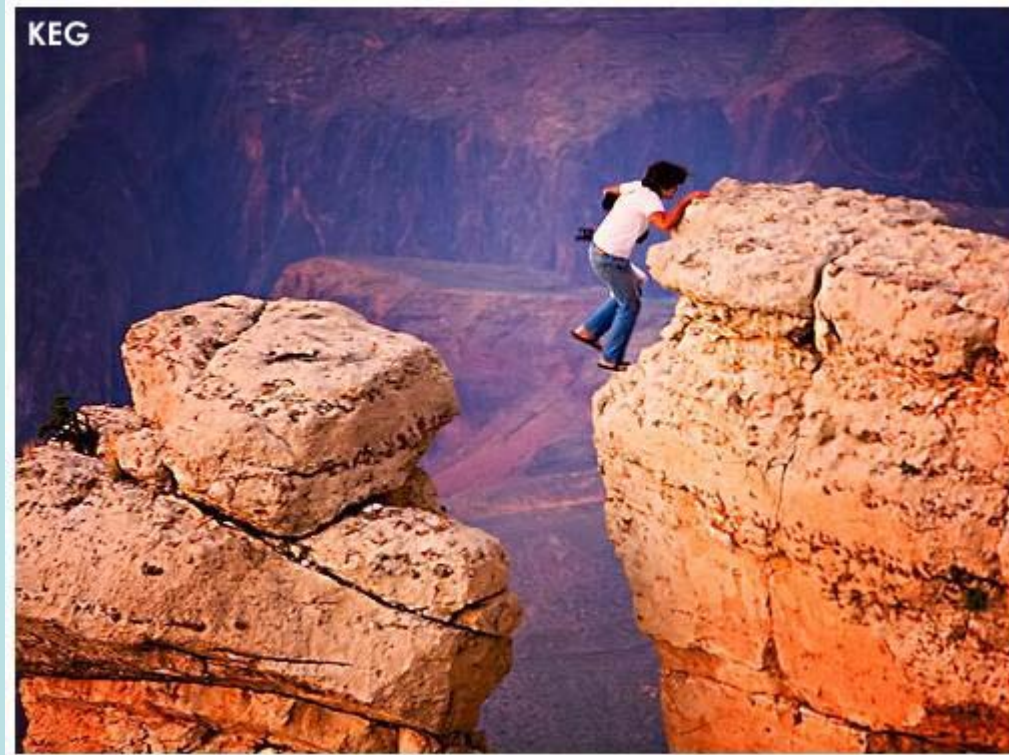
***After the sun set behind the canyon's horizon he packed his things (having only one hand available) and prepared himself for the jump. This took about 2 minutes. At that point he had the full attention of the crowd.***

- ***This is the point of no return. After that, he jumped in his flip flops...  
The canyon's depth is 900 meters (3,000 feet) here.***





# The Result



- ***Now you can see that the adjacent rock is higher so he tried to land lower, which is quite steep and tried to use his one hand to grab the rock.***

# Bowel disorder!

- *We've come to the end of this story. Look carefully at the photographer. He has a camera, a tripod and also a plastic bag, all on his shoulder or in his left hand. Only his right hand is available to grab the rock and the weight of his stuff is a problem. He lands low on his flip flops, both his right hand and right foot slip away... At that moment I take this shot. He pushes his body against the rock. He waits for a few seconds, throws his stuff on the rock, **climbs and walks away, presumably to a bathroom to change his shorts.** I know I had to change mine and I was just watching.*

# Oropharyngeal Ca

- A recent publication in the American Academy of Otolaryngology demonstrated changes in incidence of head and neck cancers over the last 15 years such that almost 80% of oropharyngeal cancers (tonsillar fossa and base of tongue) are now HPV related. Most are thought to be sexually transmitted.
- This is not to be confused with Nasopharyngeal cancers which are common in the Chinese population and related to infection with the Epstein Barr Virus(EBV).

# HPV-related Head and Neck cancers rise in Canada

– This headline from Medical Post October 4<sup>th</sup> 2011.

- HPV-related H and N cancers prevalence increases in relation to Non-HPV related cancers.
- Previously these cancers were related to Alcohol and Cigarette smoking.
- Now 80% of oropharyngeal cancer has HPV as an aetiological cause!

There is no  
vaccine  
against stupidity!





# MOLECULAR PATHOGENESIS

- The two most important HPV proteins in the pathogenesis of malignant disease are E6 and E7.
- The continued expression of both of these proteins appears to be required to sustain a malignant phenotype.
- E6 and E7 act synergistically to transform cells, although E7 is capable of transforming cells in isolation.

- While a number of HPV types can be found in the ano-genital tract, only a limited number of these viruses have been associated with cancer. The different HPV types are characterized by genotypic variations in the DNA base-sequences of E6 and E7.
- As an example, the E7 protein of HPV 16 is more oncogenic than the E7 protein of HPV 6

# E6/E7 protein

- Some of the HPV "early" genes, such as E6 and E7, are known to act as [oncogenes](#) that promote tumour growth and [malignant transformation](#).
- [E6](#) has a close relationship with the cellular protein E6-AP (E6-associated protein). E6-AP is involved in the [ubiquitin ligase](#) pathway, a system that acts to degrade proteins. E6-AP binds ubiquitin to the p53 protein, thereby flagging it for proteosomal degradation.
- **HPV associated cancers are caused by the expression of HPV's E6 and E7 proteins that bind to and *inactivate* tumour suppressor proteins [p53](#) and [retinoblastoma protein](#) (pRB), respectively, leading to malignant transformation of HPV infected cells.**
- The biology of HPV is distinct of HPV with [P53](#) degradation (inactivated by E6 instead of by genetic mutation), pRB pathway inactivation (by E7 instead of [Cyclin D1](#) amplification), and [P16](#) upregulation (over-expression instead of inactivation)

# Retinoblastoma Protein

The **retinoblastoma protein** (abbreviated **pRb**, **RB** or **RB1**) is a tumor suppressor protein that is dysfunctional in many types of cancer.

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# P53 protein

- The **p53** protein prevents cell growth and stimulates **apoptosis** in the presence of DNA damage.
- The p53 also upregulates the p21 protein, which blocks the formation of the **Cyclin D/Cdk4** complex, thereby preventing the phosphorylation of RB1 and, in turn, halting cell cycle progression by preventing the activation of **E2F**.
- In short, p53 is a tumor suppressor gene that arrests the cell cycle when there is DNA damage.

# Apoptosis-antagonizing transcription factor

- Apoptosis antagonizing transcription factor has been shown to [interact](#) with [Sp1 transcription factor](#), [POLR2J2](#), [PAWR5](#) and [Retinoblastoma protein](#).
- The protein encoded by this gene was identified on the basis of its interaction with MAP3K12/DLK, a protein kinase known to be involved in the induction of cell apoptosis.



# SYMPTOMS

- Symptoms of anal cancer include:
- change in bowel habits,
- a lump in or near the anus,
- pain with defecation
- rectal bleeding, often coating the stool
- itching or discharge
- fissure

# RISK FACTORS

- HPV Infection-high-risk types of HPV, notably HPV-16, were detected in 84 percent of anal cancer specimens.
- **Smoking**-More than half of the anal-cancer patients studied were current smokers at the time of diagnosis, as compared to a smoking rate of about 23 percent among the controls, researchers speculate that smoking interferes with a process called [apoptosis](#). Another possibility is that smoking suppresses the [immune system](#).

# More Risk factors

- Immunosuppression- often associated with HIV
- Benign anal lesions([inflammatory bowel disease](#) (IBD), [hemorrhoids](#), [fistulae](#) or cicatrices. Inflammation resulting from benign anal lesions, such as hemorrhoids and anal fistulas, may predispose to anal cancer, but a lot of people have piles and very few get anal cancer

# Treatment

- There are protocols which I will mention shortly but I would like to start with .....

# Prevention!!!!

- Vaccine against HPV is a good idea and in my opinion and in the opinion of many specialists the vaccine which is offered to teenage girls should also be offered to boys.
- Two vaccines available. Gardasil and Cervarix
- Pap smears for women and MEN ??????
  - Anal dysplasia clinics in the HIV/AIDS centres

# Treatment

- Small cancers at the anal margin and carcinoma in situ are treated by local excision provided adequate margins can be obtained.
- The majority of tumours are not suitable for local excision and the only surgical option is abdomino-perineal excision of the anus and rectum.

- Radiotherapy +/- chemotherapy has been shown to produce similar survival rates to surgery and approx 85% of patients retain anal function.
- The drugs that have been shown to increase the effect of radiation are 5-FU, Mitomycin C and Cisplatin.

# Side Effects of Treatment

- **Early reactions.** Important to distinguish between small and large bowel reactions.
- **Small bowel reactions**
  - 1) Abdominal cramps.
  - 2) Watery brown stool.
- Usually start about 7-10 days after first treatment
- May be exacerbated by chemotherapy particularly 5-Fluorouracil
- These symptoms are due to damage to the small bowel mucosa which leads to irritability and decreased absorption of bile salts and of some food and water. Treatment is aimed at slowing the transit of small bowel contents.

- **Large Bowel**

- 1) Tenesmus - feel need to go frequently, but don't achieve much
- 2) Flatus
- 3) Increased mucus in stool
- 4) Small fecal pellets

# Managing Side Effects

- Small Bowel: Diarrhoea treated with Imodium.
- Large Bowel: These symptoms are due to inflammation of the large bowel lining and are treated with stool softeners and local anti-inflammatory treatment for the rectum such as Proctosedyl suppositories.

# Later Side Effects

- **Acute skin reaction**
- Usually starts within 10-14 days of the start of treatment.
- Cortisone cream until moist desquamation after which use flomazine.
- Sitz baths - warm water no salt. Dab skin dry, don't rub



# Follow Up

- Most recurrences occur within the first two years. **Vast majority can be detected with a finger.**
- Physical examination every 6-8 weeks for 2 years. Thereafter 4 monthly until 5 years.
- If disease was present prior to treatment that was only detected by CT or MRI, this should be repeated 8-12 weeks after treatment to ensure that the disease has responded. Repeat imaging thereafter will depend on individual circumstances.

# Mr S

- Pt agreed to treatment with Chemo-Radiation.
- 5400cG in 30# with Cisplatin and then Capecitabine pre-treatment.
- He remained in BCCA for duration of his treatment.
- F/u every 6weeks for 2 yrs.

# Questions?

- But Remember.....

If you have  
something to say  
raise your hand  
and place it over  
your mouth



# The intriguing study published in Psychological Science

- [Taking a vitamin may lead to debauchery](#) Taking supplements can give people a false sense of invulnerability -- and a stronger inclination to have casual sex, skip exercising and lounge in the sun, a new study shows.