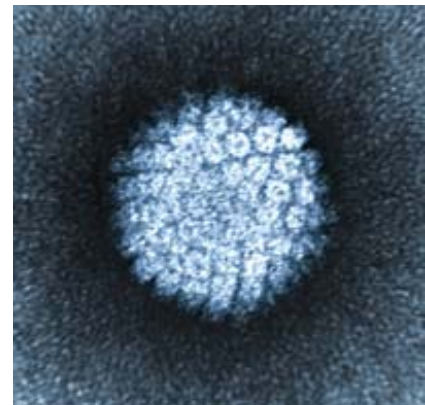


## A Virus in the Limelight - Papilloma and the Nobel Prize

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**Papillomaviruses infect keratinocytes, cells of the skin and mucosal surfaces. In humans and other animals affected by papillomaviruses, the immune system is usually effective in clearing the infection. However, persisting papillomaviruses can – over a period of years – cause warts (papillomas) and even cancer. Although other viruses have also been connected to cancer, the unequivocal link between certain human papillomavirus (HPV) types and cervical cancer is absolutely unique. These findings led to the development of both HPV testing (for diagnosis and treatment of cervical abnormalities and lesions) and the two preventative HPV vaccines available today. It is hoped that widespread use of the vaccines will reduce the incidence of cervical cancer by as much as two-thirds.**

Warts, or papillomas (benign epithelial tumors), are certainly not a new phenomenon. The Greeks mentioned them, as did the Romans and writers in medieval times. However, the cause of warts – papillomaviruses - has only recently come to light. Papillomaviruses don't share the prominence of influenza virus or the notoriety of HIV, but in the last years they've gotten their fair share of publicity. In 2006, the approval of a vaccine for human papillomavirus (HPV), the cause of cervical cancer, was met with enormous enthusiasm...and waves of controversy that are still reverberating. And two years later, Harald zur Hausen, whose findings made the HPV vaccine possible, was awarded the greatest honor a researcher can receive, the Nobel Prize. Two pretty eventful years for a tiny little virus!



Electron micrograph of human papillomavirus (HPV) © Laboratory of Tumor Virus Biology, National Cancer Institute, USA

### Papillomaviruses: the basics

- non-enveloped DNA viruses
- infect a wide range of animals (birds, rabbits, manatees, humans...)
- believed to be transferred via micro-traumas of epithelia
- replicate exclusively in keratinocytes, first targeting keratinocyte stem cells
- often infect particular body surfaces (skin or mucosal surfaces, e.g. genitals, anus, mouth or airways)
- ~130 human papillomaviruses (HPV) identified; 30–40 infect the anogenital region and are transmitted through sexual contact
- most HPV infections asymptomatic, are cleared by the immune system; some types can cause warts or cancer

Genital warts were long considered to be the result of syphilis, gonorrhea or other “venereal poison”, a mistaken belief that held until the causative agents of these diseases were identified in the late 19<sup>th</sup> and early 20<sup>th</sup> centuries. And despite widespread popular belief that common skin warts are contagious, scientists didn’t embrace the idea until the end of the 19<sup>th</sup> century. In 1907, Giuseppe Ciuffo could show that a filterable agent – most likely a virus – transmitted skin warts, and further experiments showed that the causative agents of common skin warts and genital warts are related. The viral origin of papillomas was confirmed by electron microscopy in 1949, but more extensive study of papilloma-causing viruses was largely hampered by difficulties in culturing and studying them using methods of classical virology.

In the late 1970s, molecular virology finally made papillomaviruses more accessible to researchers. When papillomavirus genomes from different human tissues were cloned and compared, it became clear that many different viral types exist and that some are regularly found in specific tissues or lesions: human papillomavirus (HPV) 1–4 in skin warts, 6 and 11 in anogenital warts, and HPV 16 and 18 among others in cervical lesions and genital tract cancers. Harald zur Hausen from the German Cancer Research Center (Deutsches Krebsforschungszentrum/DKFZ) in Heidelberg, Germany was a major contributor to the research defining HPV subtypes, and for these and other seminal findings on the role of papillomaviruses in cervical cancer, he was awarded the 2008 Nobel Prize in Physiology or Medicine.



Harald zur Hausen Nobel Prize Laureate for Physiology or Medicine 2008.

### Harald zur Hausen

- born March 11, 1936 in Gelsenkirchen, Germany
- received his M.D. from the University of Düsseldorf in 1960
- worked at the Children's Hospital of Philadelphia from 1966 to 1969 with Prof. Werner and Gertrude Henle, contributing to the novel finding that Epstein-Barr virus can transform healthy lymphocytes into cancer cells
- after returning to Germany, pursued research on human papillomavirus and cancer:
- 1969–1972, Senior scientist at the Institute for Virology, University of Würzburg
- 1972–1977, Chairman and Professor at the Institute for Clinical Virology, University of Erlangen-Nurnberg
- 1977–1983, Chairman and Professor at the Institute for Virology and Hygiene, University of Freiburg
- 1983–2003, Chairman and member of the scientific advisory board of the German Cancer Research Center, Heidelberg
- 2003–present, Emeritus professor at the German Cancer Research Center
- editor-in-chief of the International Journal of Cancer
- in 2008 awarded the Gairdner Foundation International Award and the Nobel Prize in Physiology or Medicine.

- In justifying its selection of zur Hausen, the Nobel Committee wrote:
- “Harald zur Hausen went against current dogma and postulated that oncogenic human papilloma virus (HPV) caused cervical cancer, the second most common cancer among women. He realized that HPV-DNA could exist in a non-productive state in the tumours, and should be detectable by specific searches for viral DNA. He found HPV to be a heterogeneous family of viruses. Only some HPV types cause cancer. His discovery has led to characterization of the natural history of HPV infection, an understanding of mechanisms of HPV-induced carcinogenesis and the development of prophylactic vaccines against HPV acquisition.”

### A new twist on an old “plague”

In the early 20<sup>th</sup> century, epidemiological data such as the increased prevalence of cervical cancer among prostitutes suggested a link of the cancer to a sexually transmitted agent. The cancer-causing potential of viruses had been shown; in fact, Francis Peyton Rous was awarded a Nobel Prize in 1966 for his research into the role of viruses in the transmission of some cancers (including his 1934 demonstration that papillomaviruses can cause skin cancer in rabbits). In the 1970s, many researchers focused on herpes simplex virus as the cause of cervical cancer. When Harald zur Hausen proposed in 1976 that human papillomavirus causes cervical cancer, the scientific world did not put out the welcome mat.

It took several years before zur Hausen and his research team could find the evidence they needed to support the hypothesis, namely the presence of DNA from papillomaviruses in tumor cells. In 1983 and 1984, his group was able to identify DNA from HPV 16 and 18, respectively, in cervical cancer biopsies. They could demonstrate that most cervical cancers hybridize probes of these two HPV subtypes under stringent conditions. Under less stringent conditions, even more cervical cancers bound the probes, indicating that additional related HPV subtypes can also cause cancer; indeed, while HPV 16 and 18 are implicated in approximately 70% of cervical cancers and along with HPV 31 are considered the key risk factors for cervical cancer, at least 12 additional high-risk HPV types and 12 low-risk types (which can also cause cancer) have been identified.

In later studies, zur Hausen’s group identified two genes (E6 and E7) from HPV that seem particularly fond of human DNA and may represent the key viral oncogenes. In 2006, the groundbreaking studies headed by Harald zur Hausen culminated in the release of a vaccine to fight HPV infection.



Rabbits with a papillomavirus infections may have inspired for the fictional cross between a jackrabbit and an antelope © Prof. Ch. Holliday (Lafayette College, USA)

### HPV and cancer

- According to Centers for Disease Control and Prevention (CDC, USA) estimates, 20 million people are currently infected with HPV, 6.2 million Americans get a new HPV infection each year and at least 50% of sexually active individuals will acquire an HPV infection at some point in their lives. (<http://www.cdc.gov/std/HPV/STDFact-HPV.htm>)
- So-called “high-risk” HPV types can cause a variety of cancers, including several of the anogenital tract (cervical, vaginal/vulvar, penile and anal cancers) as well as 25–30% of head and neck cancers.
- HPV infection is the cause of nearly all cases of cervical cancer.
- HPV types 16 and 18 are together responsible for 65–75 % of cervical cancer.
- Some 500,000 new cases of cervical cancer are diagnosed worldwide each year, making it the second most common cancer among women. Approximately half of affected women die. In Europe 33,500 woman are diagnosed with cervical cancer each year, and 15,000 die of it.
- More than 80% of cervical cancers occur in the developing world.
- HPV E6 oncoproteins inhibit the function of p53, a transcription factor that regulates cell cycle and acts as a tumor suppressor. The low rate of cervical cancer in Jewish women is thought to be related to p53 polymorphism.

### HPV Vaccine: controversial hope

The widespread use of Pap testing has reduced the incidence and lethality of cervical cancer in developed countries, but worldwide the disease still kills several hundred thousand women per year. According to some estimates, the HPV vaccine has the potential to reduce cervical cancer deaths by two-thirds.

It's actually highly incorrect to say “the” HPV vaccine. Two HPV vaccines are available, Gardasil (Merck) and Cervarix (GlaxoSmithKline). Both vaccines are based on hollow virus-like particles (VLPs) assembled from recombinant HPV coat proteins. They are designed to induce virus-neutralizing antibody responses that prevent initial infection with the HPV types represented in the vaccine, cervical cancer-causing HPV 16 and 18 in both vaccines as well as HPV 6 and 11 (cause 90% of genital warts) in Gardasil. The vaccines are preventative; HPV types already present are not eliminated. For this reason the vaccines, which have been shown to be highly effective in preventing genital warts and precancerous lesions caused by the HPV types in the vaccines, are especially recommended for girls 11 to 12 years of age and older who are not yet sexually active.

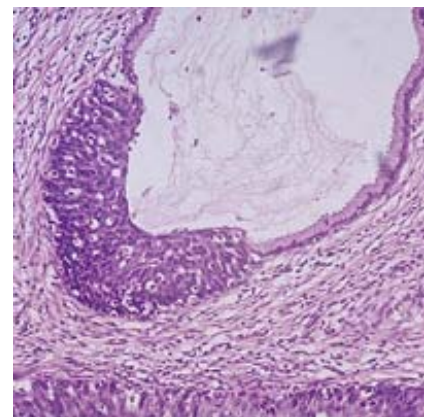


HPV vaccination - not for girls only! ©AOK-Mediendienst

Both Gardasil and Cervarix have been approved in the European Union, Australia and other countries, in many cases under expedited review. In the United States, Cervarix is still under consideration, with approval expected in 2009 (Gardasil was approved in 2006). The enormous

enthusiasm for the potential of the vaccine has Gardasil and Cervarix flying high, but there is some major turbulence in the skies. In the United States, a massive lobbying effort by Merck to make the ~\$400 Gardasil regimen a mandatory school vaccination backfired severely, inducing opposition from many sides and deepening the distrust in pharmaceutical companies. And in Germany, a group of 13 physicians has issued a written request to the governmental vaccination board (STIKO) to reassess its recommendation for HPV vaccination (“Statement of 13 German scientists on the HPV-vaccine”; link provided below). The biggest issue: critics argue that it is unclear from the available data how the claimed effectiveness of the vaccine (>70% in preventing cervical cancer) was calculated, and STIKO didn’t consider more recent analyses in its decision (more about the STIKO position can be found under a link below). As in the United States, many in Europe feel that immense lobbying efforts by the pharmaceutical companies may have been effective in pushing rapid approval of the vaccines and recommendations – or mandates – for their use.

That said, despite the absence of long-term data (cervical cancer often develops 10 to 15 years after HPV infection), many physicians and scientists, including Harald zur Hausen himself, believe strongly in the effectiveness of the HPV vaccines, and it seems absurd to wait years for long-term data before implementing a vaccine that holds so much promise to save lives and reduce human suffering. However, there are additional points of debate. How can a vaccine that costs more than \$400 be effective in reducing cervical cancer deaths worldwide? Remember, more than 80% of women with cervical cancer live in developing countries. And even in developed countries, the costs of such a vaccine may be debilitating to health care systems or could keep many women from getting it



Cervical gland showing an area of high grade epithelial dysplasia (CIN3). © Dr. John Hayman, University of Melbourne, Australia

if they must pay themselves. In addition, because of the differences in HPV types between geographical regions, the vaccines (with HPV 16 and 18) are likely to be most effective in Europe/North America and least effective in sub-Saharan Africa. Vaccines covering more types are needed (a “nine-valent” vaccine from Merck with the name V503 has entered international phase III trials, with estimated completion in 2013). Finally, should boys be vaccinated, too? After all, genital warts occur in both males and females to the same degree (and are passed from one to the other), and anal cancers as well as a significant proportion of head and neck cancers are caused by HPV.

Regardless of the controversy nagging the HPV vaccine, the remarkable contributions of Harald zur Hausen remain above all doubts. While other infectious agents have been linked to cancer (Hepatitis B and liver cancer, *Helicobacter pylori* and stomach cancer, Epstein-Barr virus and Burkitt's lymphoma), the direct link between HPV and cervical cancer is absolutely unique. And it just may be the hope for near eradication of one of the cancers of human life.

### References and additional reading:

- Human Papillomavirus Infections in Dermatovenereology by Gerd Gross and Geo von Krogh (see [books.google.com](http://books.google.com))
- Infections causing Human Cancers by Harald Zur Hausen, James G. Fox, Timothy C. Wang, Julie Parsonnet (see [books.google.com](http://books.google.com))
- The Nobel Lecture and an interview with Harald zur Hausen can be found under [http://nobelprize.org/nobel\\_prizes/medicine/laureates/2008/](http://nobelprize.org/nobel_prizes/medicine/laureates/2008/)
- A variety of HPV fact sheets are available from the Centers for Disease Control and Prevention (CDC) under <http://www.cdc.gov/STD/HPV/default.htm>
- The Statement of 13 German scientists on the HPV-vaccine (Stellungnahme zur Wirksamkeit der HPV-Impfung) can be downloaded under <http://www.uni-bielefeld.de/gesundhw/ag3/downloads.html>
- Information about the HPV vaccine from the Robert Koch Institute, including answers to questions regarding patient safety and the approval procedure, are available under [http://www.rki.de/cln\\_091/nn\\_494662/DE/Content/Infekt/Impfen/ImpfenA-Z/HPV/HPV\\_ImpfenA-Z\\_ges.html](http://www.rki.de/cln_091/nn_494662/DE/Content/Infekt/Impfen/ImpfenA-Z/HPV/HPV_ImpfenA-Z_ges.html)
- Information about the rabbit papillomavirus infection: <http://ww2.lafayette.edu/~hollidac/jacksforreal.html>