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EUGENE GARFIELD
INSTITUTE FOR SCIENTIFIC INFORMATION®
3501 MARKET ST., PHILADELPHIA, PA 19104

All Sorts of Warts—Separating Fact from Fiction. Part 1. Etiology, Biology, and Research Milestones

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Warts are common, contagious, usually benign epithelial papillomas caused by the human papillomavirus. In Part 1 of this two-part essay, the etiologic, biologic, and clinical characteristics, as well as malignant transformation in warts, are discussed. Using the ISI® database, we've identified the most active research fronts during the past decade and their relationship to other medical problems. The key players in this international field include Gérard Orth, Lutz Gissmann, and Harald zur Hausen. Milestone papers and *Citation Classics*® commentaries also are discussed. Part 2 will cover treatment and spontaneous regression. We'll also list the journals that publish wart research.

For some reason there has always been a certain mystique about warts. I can remember as a child hearing a lot of old wives' tales about how people got warts. According to one of the more popular theories, touching a toad or frog would cause warts to grow on your hands.

There are a lot of misconceptions and misunderstandings about those strange bumps that appear on the body. Wart sufferers usually are embarrassed by them, and those without warts generally are repulsed by them. Unfortunately, even among the educated, few realize that warts, like the common cold, are caused by a virus. By contrast, who is embarrassed to suffer from a cold, even with its visible symptoms? Also unknown to most of the general public is that these seemingly benign nuisances have the potential to become a serious health problem.

In this two-part essay, we are going to try to dispel some of the myths about warts and answer some common questions. What actually causes them? How are they best treated? And of greater importance to *Current Contents*® readers, who are the leaders in wart research? As you'd expect, we'll review their work and the impact they've had on the field. We'll also identify the most active research fronts related to warts.

Description

Warts are common, contagious, usually harmless epithelial tumors caused by one of the human papillomaviruses (HPVs), members of the family Papovaviridae.[1] Papillomaviruses infect humans and a number of animals, including rabbits, sheep, cattle, horses, dogs, monkeys, and deer. The viruses are generally species specific, that is, each virus will infect only a specific target host. (One exception, however, is bovine papillomavirus, which has a larger host range than other papillomaviruses and can infect horses, hamsters, and rats, as well as cattle.) As Gérard Orth, Gustave-Roussy Institute, INSERM, Villejuif, France, points out, one of the drawbacks in studying papillomaviruses is that they do not grow *in vitro*. However, the use of DNA recombinant technology has helped researchers partly overcome this problem.[2]

Papillomas, which are benign tumors, are produced in their hosts by the viruses. They contain variable amounts of infectious virus. The word papilloma is derived from *papilla*, meaning pimple or pustule, and the suffix *-oma*, which denotes a tumor or neoplasm.[3] In the wart literature the terms wart and papilloma are used synonymously. Here we will do the same.

Direct skin-to-skin contact is the most common means of wart transmission. The virus enters the skin through small surface abrasions. Nailbiting, which traumatizes the skin, can aggravate warts on the fingers and make them extremely difficult to treat. Subsequent to their infection through a microtrauma, epidermal basal cells proliferate either downward, giving rise to endophytic warts like plantar warts, or upward, giving rise to exophytic warts like common warts.[2] Papillomavirus infection probably occurs in the basal layer of the epidermis. Warts not only are contagious, but they also can spread from one part of the body to another. For example, warts can be transmitted to the face or feet from the hands. Children with hand warts who suck their thumbs can infect the facial areas around the mouth and on rare occasions the tongue and mucous membranes. However, hand warts are rarely transmitted to the anogenital area.

Public bathing and changing facilities are common sources of plantar warts. The rough, nonslip surfaces that surround many swimming pools and shower areas act as abrasives that rub infected material off of plantar warts. Papillomavirus particles have a very simple structure and are considered to be stable. They are shed in the environment inside resistant, cornified cells. In the absence of *in vitro* studies it is difficult to evaluate their susceptibility to specific disinfectants. Thus, the use and effectiveness of chlorine or other agents is questionable in regard to killing and controlling the spread of the virus in these areas.[2] HPV does not survive long on objects, and, although it is not likely, wart infection occasionally may be picked up from contaminated objects, such as golf club handles at rental driving ranges.

Prevalence

Dermatologist Mary H. Bunney, Royal Infirmary, Edinburgh, UK, points out that approximately 10 to 25 percent of patients who visit a dermatologist do so for warts.[4] (p. 1) Certain groups seem to be at higher risk than others. Common warts are seen most often in school-age children and adolescents, especially before puberty, but rarely in the elderly. Children under the age of two are rarely affected, according to Stephen E. Gellis, Tufts University Medical School, Medford, Massachusetts.[5] However, the entire population is at risk. Genital warts are mainly seen in sexually active adults.

Holger Kirchner, Institute of Virus Research, German Cancer Research Center, Heidelberg, Federal Republic of Germany (FRG), suggests several reasons for the increased incidence of warts in children. He believes that a child's skin is different from that of an adult and is more susceptible to viruses, possibly as a result of hormonal influences. And, Kirchner postulates that some children may have a defective immune defense mechanism before puberty and thus cannot fight the HPV.[6] Another possible explanation for the increased incidence of warts in children may be that adults acquire immune protection after a first infection during childhood with these widespread viruses.[2] Dermatologist Walter B. Shelley, Medical College of Ohio, Toledo, adds that "warts seem to be one of those universally acquired viral infections of childhood, in many cases not even apparent to the child or parent. Accordingly, the opportunity for transmission from child to child is great. The clinical problem is seen in those with immune deficits, either genetic or acquired."[7]

Injury and irritations seem to increase the chances of contracting warts. Those in some injury-prone occupations, such as butchers, fishmongers, and poultry processors, are especially susceptible. The hands of these workers are constantly macerated because they are immersed in water and other fluids. Thus, the risk is increased. Not surprisingly, the resulting warts are often called butcher's warts.

Patients with deficiencies in cell-mediated immunity (those with AIDS, Hodgkin's disease, malignant lymphoma, and chronic lymphocytic leukemia) frequently have warts. Individuals taking immunosuppressant drugs, particularly renal allograft recipients, are prone to widespread and resistant warts. A compromised immune system makes it difficult for the body to fight the

HPV infection. Next to herpesviruses, HPV infections are the most frequent viral complications affecting immunosuppressed individuals.[6]

Warts and Immune Deficiencies

Related to this topic is the research front entitled "Papillomavirus in renal allograft recipients" (#86-7565). Two articles are core to this cluster. One, by Marvin Lutzner, Pasteur Institute, Paris, and colleagues,[8] was the first paper to report findings of skin lesions induced by human papillomavirus type 5 (HPV-5) in two immunosuppressed renal allograft recipients. HPV-5 had previously been found only in patients with the rare skin disease epidermodysplasia verruciformis (EV), which often becomes malignant. (HPV types and EV will be discussed at greater length later.)

The second core paper, written in 1975 by Warwick L. Morison, St. Helier Hospital, Surrey, UK,[9] reviews results of a study of patients with immune deficiency disorders. Morison found that patients with cell-mediated immune deficiency, specifically Hodgkin's disease, were more susceptible to warts and herpes zoster infections than were patients with humoral immune deficiency, for example, those with multiple myeloma. This disease is characterized by marrow plasma cell tumors and overproduction of monoclonal immunoglobulins.[10] In humoral immune responses, immunity is mediated by antibodies produced by B cells, or B lymphocytes, which are derived from bone marrow. This differs from cell-mediated immunity, where the immune responses are controlled by T cells, or T lymphocytes.[11]

Milestones in Wart Research

Celsus was the first to discuss warts, in 25 AD. In 500 AD Greek and Roman physicians wrote about genital warts, which apparently were quite common. They were the first to note the sexual transmission of genital warts.[4] (p. 5) At that time, however, attention obviously was centered more on treating warts rather than discovering what actually caused them.

It was not until 1891 that Joseph F. Payne, a physician at St. Thomas' Hospital, London, recorded the infectious nature of warts. In his classic paper "On the contagiousness of common warts," Payne described how warts grew on his own thumb after he had scraped off the surface of a child's wart. Payne concluded that "fresh warts are produced by local inoculation of some pathogenic material derived from an existing one."[12] Further evidence of the contagiousness of warts was supplied in 1894 simultaneously by C. Licht[13] and Parisian pediatrician Gaston Variot,[14] who experimentally transferred warts to volunteers by injecting them with ground wart tissue.

In 1907 G. Ciuffo was the first to associate viruses with wart diseases.[15] In his experiments Ciuffo produced warts on his own hand by injecting himself with a filtrate that had been passed through a pore so small that only viruses could be involved.

Similar research was done in rabbits by Richard E. Shope, Department of Animal and Plant Pathology, Rockefeller Institute for Medical Research, Princeton, New Jersey, in 1933. Shope found wild cottontail rabbits with naturally occurring warts. He found that the wart-producing agent was, in fact, a virus much like the viruses that produced papillomas in humans, cattle, and dogs. Shope also exhibited the contagious nature of these warts by transferring the infection to domestic rabbits.[16] These papillomas are called Shope papillomas.

Two years later Peyton Rous and J.W. Beard, Rockefeller Institute for Medical Research, New York, observed that benign, virus-induced rabbit papillomas (Shope papillomas) may become malignant papillomas, which in turn can progress to squamous cell carcinomas. Pigmented papillomas are the most likely to become malignant.[17] Rous shared a Nobel Prize in 1966 for discovering tumor-inducing viruses, a major landmark of modern medical science.

Ciuffo's findings were not corroborated until 1949, when Maurice J. Strauss and colleagues, Yale University School of Medicine, New Haven, Connecticut, using an

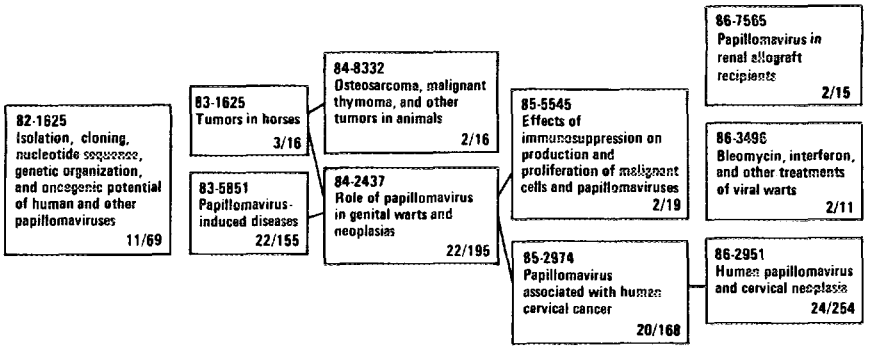

Figure 1: Historiograph tracing research on papillomaviruses, 1982-1986. Numbers of core/citing papers are indicated at the bottom of each box.

electron microscope, observed virus-like bodies in samples taken from skin papillomas.[18] This paper has been cited nearly 70 times since 1955. One year later, Strauss and coworkers identified HPV as the cause of warts.[19] Thus far, the paper reporting these findings has been cited about 50 times since 1955. However, we'll soon know its impact between 1950 and 1954 when we publish the *Science Citation Index®* for 1945-1954 later this year.

After this classic finding, research focused on the causes of the different types of warts. Evidence indicated that the same virus was responsible for all types. It was not until 1977 that Lutz Gissmann, Herbert Pfister, and Harald zur Hausen,[20] Institute for Clinical Virology, Friedrich Alexander Erlangen-Nuremburg University, Erlangen, FRG, and, independently, Orth and coworkers[21] demonstrated that there is more than one type of HPV.

The Gissmann paper[20] received nearly 140 citations from 1977 to 1987. Orth's article[21] also was cited in more than 100 publications during the same period. The two classic papers were already core articles in the 1982 research front on "Isolation, cloning, nucleotide sequence, genetic organization, and oncogenic potential of human and other papillomaviruses" (#82-1625). Two other papers by Orth and coworkers[22,23] and another authored by Gissmann and zur Hausen[24] are among the 11 core documents of this 1982 cluster. Interestingly, Orth is one of the coauthors of the article by Lutzner and coworkers[8] that we identified earlier.

Tracking Wart Research

Figure 1 is a historiograph of the research on papillomaviruses from 1982 to 1986. Several key authors mentioned earlier have published papers that are core to these topics. Research front #83-5851, "Papillomavirus-induced diseases including laryngeal carcinoma, epidermodysplasia, and cervical condyloma and intraepithelial neoplasia," has zur Hausen among its 22 cited core authors. There were 155 papers published that year that cited 1 or more of these papers.

When we performed our annual co-citation clustering exercise in 1984, this topic was easily identified and named "Role of papillomavirus in genital warts, cervical cancer, and other neoplasias" (#84-2437). Four core papers carried over into the new 1984 cluster. The most-cited core paper for this topic is the paper by M. Dürst, Institute for Virology, Freiburg in Breisgau University, FRG, and coworkers.[25] Remarkably, this 1983 *Proceedings of the National Academy of Sciences of the USA* article has already been cited in more than 210 papers. In this study, HPV-16 was identified as the most prevalent HPV type found in malignant tumors of the uterine cervix. Both Gissmann and zur Hausen are coauthors of this paper.

By tracking the core articles that we identify each year, we can follow the twists and

turns of the literature. In 1985 there were about 170 articles published on "Papillomavirus associated with human cervical cancer" (#85-2974). Dürst, Gissmann, and zur Hausen were among the 20 core authors in this cluster. There are two other core papers worth noting. The first is by C.P. Crum, Columbia University College of Physicians and Surgeons, New York, and coworkers (including Gissmann).[26] M. Boshart, Institute for Virology, Freiburg in Breisgau University, and colleagues (including Gissmann and zur Hausen) published the second.[27] The Crum article, which has been cited more than 100 times from 1984 to 1987, identified HPV-16 in cervical neoplasms. The Freiburg paper has been cited in more than 120 publications during the same period. A new type of papillomavirus DNA (HPV-18) was isolated from malignant cervical cancer biopsy specimens.

In 1986 over 250 papers were published on "Human papillomavirus and cervical neoplasia" (#86-2951). This is the largest of the warts-related annual clusters. Of the 24 core papers identified, 3 are by Gissmann,[28-30] 2 by Pfister,[31,32] and 2 by zur Hausen.[33,34] How these research fronts are related to the topic of cancer and warts will be discussed later in the section on "Malignant Transformation."

How the Research Areas Are Related

Figure 2 is a C2-level map showing the links between C1-level research fronts that deal with papillomaviruses. Two of these 1986 fronts, points 7565 and 2951, were discussed earlier. Another, 5033, will be discussed later. The others concerning treatment will be covered in Part 2 of the essay.

Biological and Clinical Manifestations

As Gissmann noted, clinically there are a variety of different types of warts: common warts, plantar warts, mosaic warts, plane warts, anogenital warts, lesions (for example, brownish or reddish macules or papules) in EV patients, and laryngeal papillomas.[35] It is also necessary to add to the list Bowenoid papules and Bowen's disease of the external genitalia (which are papillomavirus-associated genital lesions considered to be precancerous and which may evolve into invasive cancers but which are not warts per se) and cervical intraepithelial neoplasia, so-called atypical condylomas.[2] Each type has its own distinguishing characteristics.[4] (p. 18-20) The types of warts can be grouped into two general categories: those affecting the skin and those found on contiguous mucous membranes.[5]

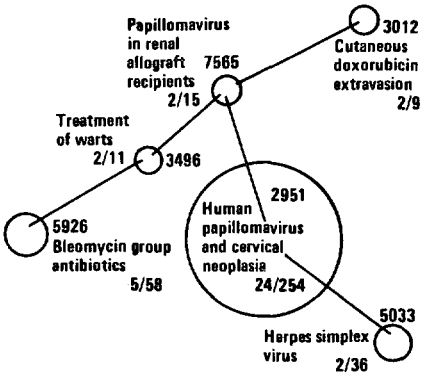

Figure 2: Multidimensionally scaled map for C2-level research front #86-0825, showing links between 1986 C1-level fronts dealing with papillomaviruses. Numbers of core/citing papers for each C1 front are shown after the name.

Each HPV type seems to cause a characteristic clinical manifestation. This hypothesis was first proposed in 1977[21] and later confirmed in 1978.[22] Yet, as T.F. Mroczkowski and C. McEwen, Tulane University School of Medicine, New Orleans, Louisiana, indicate, certain warts have been found to contain more than one type of HPV.[36] Approximately 50 types have been identified. However, new HPV types continue to be discovered. K.T. Smith and M.S. Campo, Papillomavirus Research Group, Beatson Institute for Cancer Research, Glasgow, UK, explain how HPV types are distinguished from each other. The classification is based on the lack of significant nucleic acid homology between different virus types. The viral DNA is composed of two strands with complementary (homologous) nucleotide sequences. In distinguish-

Table 1: Types of warts and associated HPV types.

Type of Wart	Frequently Associated HPV Type(s)	Common Site(s) of Appearance
Common wart (verruca vulgaris)	HPV-1	Hands
Mosaic warts	HPV-2	Soles and heels of feet; palms; knuckles; around fingernails
Plane warts (flat warts, verruca plana)	HPV-3, HPV-10	Face; arms; backs of hands of children and young women
Plantar warts (verruca plantaris)	HPV-1	Plantar surface of foot
Butcher's warts	HPV-7	Hands of butchers, poultry workers, veterinarians
Anogenital warts	HPV-6, HPV-11	External mucosal surface of genitalia; anorectal area of both men and women; lower genital tract of women
Epidermodysplasia verruciformis (EV)	HPV-3, HPV-5, HPV-8, HPV-17, HPV-20	All parts of skin
Laryngeal papillomas	HPV-6, HPV-11	Vocal cords and larynx of children and some adults
Genital intraepithelial neoplasia	HPV-16, HPV-18, HPV-31, HPV-33	Same as those for anogenital warts

ing HPV types, a viral isolate is considered to be an independent virus type if it shares less than 50 percent of nucleic acid homology with other papillomaviruses.[37] Table 1 shows the links between different HPV types and the different kinds of warts they produce.

Verruca vulgaris, or the common wart, is the most frequently encountered wart, and, while found most often on the hands, it actually can appear anywhere on the skin. Mosaic warts, which are very resistant to treatment, are typically seen on the soles and heels of the feet and on the hands. Plane warts appear most often on the backs of hands of children and young women, but rarely on those of men. They usually are multiple and increase in size and number before disappearing. Painful plantar warts often occur in young adults on the pressure points of the plantar surface of the foot.

Condyloma acuminata (genital warts), cervical flat condylomas, and genital intraepithelial neoplasia grow on the genital mucosa. Genital condyloma acuminata usually occur on the penis and sometimes on the scrotum, anus, vulva, vagina, and cervix. Occasionally, condyloma acuminata appear on extragenital locations such as the nipple, urethra, bladder, and oral cavity, note Alexander Meisels and Carol Morin, Saint-Sacrement Hospital, Quebec, Canada.[38] Pregnancy aggravates genital warts, causing them to become larger and multiply. Genital warts generally are seen in sexually active adults. When condyloma acuminata are found in children, sexual abuse should be suspected, although children with hand warts can spread the infection themselves, or a caretaker with warts could unintentionally infect the child. However, a physician should look for further signs of sexual abuse in these cases.[5]

A very rare skin disease, EV, mentioned earlier, is characterized by generalized plane warts and other flat lesions. In 1972 Stefania Jablonska and coworkers, Warsaw School of Medicine, Poland, reported on a study showing that HPV is responsible for the cutaneous lesions in EV and does not simply accompany them.[39] More than 15 HPV types, among them HPV-3, -5, -8, -17, and -20, are associated with this condition (Table 1). These warts can undergo malignant transformation when exposed to sunlight. In fact, HPV is necessary for the initiation of this process.[39] (More will be said about this later.)

Laryngeal papillomas, which grow on the vocal cords and larynx, affect children and adults and can obstruct airways. While they are seen as frequently in both groups, they are more distressing in children.[2] Emergency surgery usually is required. Unfortunately, these warts often recur. M.E. Bender, Department of Dermatology, University of Minnesota Medical School, Minneapolis, explains that HPV-induced warts and tumors may reappear after all clinically detectable signs of warts are removed because latent HPV DNA apparently can persist in susceptible cells for several months without showing any signs of recurrence. If all of the HPV infection is not removed or destroyed, then the dormant HPV can become active and stimulate wart growth at a later time.[40]

There seems to be a connection between laryngeal warts in children and genital warts in mothers at the time of their deliveries.[4] (p. 20),[5] D.J. McCance, Department of Microbiology, United Medical and Dental Schools of Guy's and St. Thomas' Hospitals, London, postulates that the virus may be transmitted to infants in aspirates (fluids in the womb that the baby may inhale) during vaginal deliveries in women who have genital wart infections.[41]

Malignant Transformation

Unfortunately, some benign warts, including genital and laryngeal papillomas and the genital HPV-associated lesions known as intraepithelial neoplasia (Bowenoid papulosis, Bowen's disease, and cervical intraepithelial neoplasia) have the potential to become malignant. Normal skin warts are generally harmless. However, some benign lesions in both humans and animals can undergo malignant transformation, also referred to as malignant conversion. In 1980 Orth and coworkers were the first to describe a connection between warts and malignancy. They found HPV-5 in squamous cell carcinomas in EV patients.[42] This article has already been cited in 150 subsequent publications.

According to zur Hausen, who also investigated the link between HPV and cancer, specific types of papillomaviruses can develop into specific malignant tumors. He also postulated that one papillomavirus alone is not capable of triggering malignant conversion. In order for a papilloma to become a carcinoma, an interaction with some type of chemical or physical carcinogen is necessary.[43] Mroczkowski and McEwen believe that there is a multiple-factor relationship between hereditary disposition, susceptibility to papillomavirus, and possible changes in cell-mediated immunity caused by ultraviolet radiation.[36] However, not all papillomas subjected to these influences will become malignant.

Smith and Campo, in their article in *Anticancer Research*, indicate that conversion of human papillomas into squamous cell carcinomas has been seen in people with EV, laryngeal papillomas, and anogenital condylomata.[37] Normal warts generally do not become malignant. However, Shelley, mentioned earlier, and Margaret G. Wood, University of Pennsylvania School of Medicine, reported the first case of a patient in whom common warts repeatedly underwent malignant change over a period of years.[44] Malignant transformation of plantar warts and common hand warts that are caused by HPV-1 and -2 or -4, respectively, is unknown. Flat subclinical warts are the most dangerous because they do not look like warts. However, they are the ones with the greatest malignant potential. Bunney, mentioned at the onset of this essay, pointed out that not every individual who carries the *potential* carcinogenic virus will develop cancer.[45]

Variable HPV Potential

Individual HPV types have different oncogenic potentials. HPV-16 and -18 exhibit the strongest links to genital cancer. In fact, HPV-16 is the most striking example of viral specificity for malignant tissue.[37] HPV-5, -8, -16, -18, -31, and -33 are the most likely virus types to undergo malignant transformation.[36] EV patients seem to be at especially high risk of developing skin cancer. HPV-5 is the most likely HPV type involved, converting the papillomas to

squamous cell carcinomas. The carcinomas appear predominantly on areas of the body exposed to the sun, although some have also been found on unexposed skin.

Warts of renal allograft patients also are susceptible to malignant transformation. HPV-5 is implicated in these individuals as well. Lutzner was the first to uncover HPV-5 in renal allograft patients.[8] Until this discovery, the virus had been seen only in EV patients.

Laryngeal papillomas caused by HPV-6 and -11 also can become malignant. These papillomas in children were usually treated with X rays until it was discovered that the X-ray treatment led to malignant conversion later in life.[43] Apparently, there is some type of synergism between HPV infection and X-irradiation. Twenty percent of laryngeal papillomas in adults undergo malignant transformation. Heavy smoking seems to be a contributing factor here.

A group of HPV types is involved in genital cancers and may be sexually transmitted since they are found in benign and malignant lesions in both men and women. Cervical lesions are the most common manifestations of sexually transmitted HPV infections in women. Meisels and Morin were the first to note the frequent coexistence of condylomata caused by sexually transmitted HPV and dysplasia and neoplasia in cervical squamous epithelium.[38] In a 1986 article, Philip G. Toon, North Manchester General Hospital, UK, and colleagues reported an association between HPV-16 and both cervical intraepithelial neoplasia and cervical cancer.[46] HPV-16, -18, -33, -35, and -39 are the most frequent HPV types associated with malignant genital cancer.

Gissmann and zur Hausen characterized HPV-6 as the most common HPV type that is found in condylomata acuminata. The 1980 article describing their work was one of the core papers in #82-1625 and has been cited 70 times thus far.[24] In a 1983 paper Gissmann and colleagues reported on their findings of HPV-11 DNA in condylomata of the cervix.[30] This article is core to research fronts #84-2437, #85-2974, and #86-2951 (Figure 1).

Existing evidence indicates that both men and women with genital HPV infections are at risk of cancer. Those with HPV-6 and -11 infections are at low risk, while those with HPV-16, -18, -31, and -33 are at high risk. Smoking and herpes simplex virus infections, according to zur Hausen, may be the "initiating" events that lead to genital malignant transformation.[43] We've identified one small research front, "Herpes simplex virus" (#86-5033), relevant to this topic (Figure 2).

This concludes Part 1 of this essay. We've discussed the different types of warts, their etiology, and their potential transformations. The concluding part of this review will cover ancient and modern treatments as well as spontaneous regression of warts, when for some unknown reason they disappear by themselves. We'll also identify the journals that publish most of the literature on this multidisciplinary problem.

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