

# Historical pearls of HPV research: from condyloma to cervical cancer

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## SUMMARY

The oldest discovered human papilloma virus (HPV) infection in an ancient Egyptian mummy testifies that there is still much to unearth in its history. The Graeco-Roman world recognized venereal infections, and its nomenclature is still valid concerning HPV lesions. Western Europeans, eons later, created various theories for HPV evolution. Animal experiments during the 19<sup>th</sup> century had a profound impact for the understanding

of HPV. In the late 20<sup>th</sup> century the carcinogenic properties of the virus had been clarified. This historical review presents the most important figures and discoveries in HPV research.

*Keywords:* Sycosis, ficus, acuminata, cervical cancer, oropharyngeal cancer.

## INTRODUCTION

Papillomaviridae, formerly known as Papoviridae, constitute a family of double stranded circular DNA viruses named Human Papilloma Virus (HPV). Members of the HPV family are known to infect both humans and animals. More than 300 papilloma virus types and subtypes have been identified, reported and meticulously analyzed. Numerous scientific studies of specimens derived from mammals, birds, reptiles and vertebrates concluded that most species have a wide variety of specific virus subtypes. Approximately 200 virus strains invade and infect human cells and instigate a host-immune response. Transmission occurs via direct contact with contaminated skin or mucous membranes [1-3]. The genome of more than 300 papilloma viruses has been fully analyzed in extreme detail. The papilloma virus infiltrates cells of the skin and mucous membranes and promotes an incessant and discordant proliferation of the infected cells. Shortly after the infec-

tion the viral DNA is adopted by the host cell and integrated in its genome. It consists of 7200- 8000 base pairs and 72 capsomeres that comprise each virion. Apart from skin, Papillomaviridae colonize mucous membranes of the genital tract as well as the upper respiratory tract in men and women [4, 5]. Initially HPV was identified as a cause of venereal diseases. Later on, characteristic skin lesions (warts) and precancerous tumors were associated to HPV infections. Moreover, many papillomaviruses have been linked to a higher cancer risk [6]. Today many studies have proven the correlation between papillomaviridae and head and cervical cancer [7, 8]. Nearly all cases of cervical cancer arise by cause of HPV infections. HPV 16 and 18, which are characterized as high-risk virus types, account for as much as 70% of malignancies. Sexual behaviour and activity play a significant role not only in regard to the contagion of the virus but also in the efficiency of any preventative measures such as immunization. Nowadays elective vaccination against human papillomavirus comprises a meaningful and successful strategy against HPV infections and the development of HPV-associated cancers. The implementation of widely applied vaccination programs against HPV tremendously contributes to the prevention of genital and cervi-

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cal cancer in women [9, 10]. Preliminary studies have established proof of the efficacy of the combination of early immunization as well as repeated Pap-smears in preventing cervical cancer. Co-testing women with a Pap-smear and an HPV test, which identifies the presence of viral genome in human cervical epithelial cells, is proven to dramatically decrease the false-negative rate. Moreover, cervical cytology is an indispensable mean regardless of HPV vaccination status. Thanks to the widely performed vaccination for HPV health-care systems and medical guidelines appear to be shifting their focus from secondary (Pap smear cervical cytology) to primary prevention of HPV-related diseases [11].

This historical review aims at unveiling evidence that HPV infections were known far before they were first mentioned in contemporary literature (19<sup>th</sup> century). Although the discovery of elucidating information about the function and effects of an HPV infection were firstly described during the 19<sup>th</sup> century, various sources indicate the diagnosis and recognition of HPV infections early on. The family is quite old, scattering clues of existence through time. Historical pearls regarding human papilloma virus infections are described in length.

## ■ PEARLS

Medicine in ancient Greece originated since the Bronze age as various Mycenaean Tablets testify [12]. Dermatology held a special position, especially in “Corpus Hippocraticum” in Classical era, while infectious penis diseases were also highly noted [13, 14]. Condylomata acuminata or venereal warts had been recognized as infectious diseases of the lower genital tract during the Greek-Roman historical period. However, physicians of the aforementioned era classified HPV genital infections as sexually transmitted, such as syphilis and gonorrhoea [15, 16]. Research has so far revealed that the terms “condyloma” and “sycosis” were both interchangeably used to describe cauliflower-like tumors of small size, arising in the genital area and potentially along with the inner surface of the thighs. Genital and anal warts were vividly described during the Greek-Roman historical period as cauliflower masses transmitted among people through sexual intercourse [17]. Among the disciples of Hippocratic medicine Condylomata acuminata were identified more as a disease of

the anus rather than a disease of the genital area [18]. Linguistically, the term “condyloma” is derived from ancient Greek, meaning a round tumour, while “acuminata” comes from Latin, a term used for “sharp points”. During the Greco-Roman period genital warts were referred to as “ficus” meaning fig due to its similarity to an open fig, or as “thymus”, having the shape of leaves of the plant thyme (Greek: θυμάρι, “thymari”) [19]. This term was first coined by Aetius Amidinus (502-575 AD) during the Byzantine Period of the Hellenic peninsula [20].

Roman encyclopedist Aulus Cornelius Celsus (ca 25BC-50AD) in his work “De Medecina” distinguished three types of dermal infection:

1. the “acrochordon” which appeared exclusively in children and usually spontaneously regressed over the course of weeks to months,
2. the “thymion” which was a papillomatous and highly vascular lesion that could arise in the genitalia,
3. the “myrmecia”, a usually painful lesion located on the soles of the feet, currently known as a plantar wart [21].

A plethora of satirical poems were dedicated to warts, such as those of the Latin poet Martial (1st century AD). In this regard warts were considered to be the result of promiscuous and excessive sexual behaviour [22]. Hippocratic disciples devised therapeutic ointments for topical use. Genital HPV infections, which should first be differentiated from aphthous ulcers of the genital region, were conservatively treated by Hippocratic physicians. They recommended the application of a topical solution consisting of a mixture of almonds and bovine medulla. This concoction was initially boiled in water. Flour was subsequently added in order to make it into a viscous mush that could be locally applied on the affected areas of the genitalia. Condylomas were further cleansed with water boiled with myrtle and steam [23]. “Myrmecia” on the other hand was a term applied to plantar warts. In Greek “myrmecia” was the equivalent word for anthill [19]. The resemblance of these superficial skin lesions is what inspired ancient Greek physicians to name it after ant nests. Furthermore, “sycosis” was also used by Greek physicians. “Sycosis” distinguished soft dermal lesions in areas of the human body outside the genital region and the anus, such as the eyelids. Finally, “condyloma” referred to a completely different

medical entity. It was used by ancient Greek doctors in order to refer to bony prominences [24].

The terms "fig" and "condyloma" survived in modern times and were identified with papillomas (benign slightly raised skin lesions). These terms were repeatedly mentioned in the works of Guido Lanfranchi (ca 1250-1306) and Guglielmo da Saliceto (1210-1277). During Medieval times, sexually transmitted diseases were vaguely described. However, the uncontrolled spreading of syphilis during the 15th century led to an increased interest surrounding venereal diseases. Syphilis, gonorrhoea and genital warts were not differentiated from one another. They shared a common cause, the "venereal poison" [25]. "De Morbis Cutaneis", the work of famous English surgeon Daniel Turner (1667-1741) on dermatological diseases, includes a detailed and unique theory around the development of papillomas. Daniel Turner recognizes that they probably are "solidified nutritious juices", which flow out of skin areas containing damaged nerve filaments [26]. Although the eminent Scottish surgeon John Hunter (1728-1793) explicitly describes the morphology of warts in his work "Treatise on the Venereal Disease", he advises contemporary doctors to perceive a wart as a sign of syphilis. In this case, John Hunter confused condyloma lesions or syphilis plaques- with genital warts [27]. Esteemed physicians such as Benjamin Bell of Hunthill (1749-1806) and William Pirrie (1807-1882) maintained refuting theories [28]. William Pirrie considered warts a result of gonorrhoea [29]. Nonetheless, Aimé Martin (1781-1844) from Lyon was the first physician in history to claim there was no correlation between venereal diseases and warts. For him warts were a form of local skin irritation [25]. Joseph Frank Payne (1840-1910), an English doctor and medical historian along with German dermatologist Joseph Jadassohn (1863-1936) suspected that warts had an underlying infective nature. Both physicians had recognized that warts could be transmitted from one person to another [30, 31].

In 1842, an analysis published by the Italian physician Domenico Antonio Rigoni-Stern concluded that death due to cancer of the uterus was very rare among virgins and nuns, contrary to married women and widows. Moreover, he demonstrated a rather extensive widespread of the disease. Rigoni-Stern became the first scientist to link the prev-

alence of cervical cancer with sexual activity and human behaviour [32,33]. Among many medical writers of the 19<sup>th</sup> century, the belief that genital warts were caused by irritation of the epidermis by various agents such as dirt, animal contact, sexual masturbation, decomposed sebum and genital discharges was vastly supported. This "miasmatic" theory of a non-specific irritant was widely accepted for many years to follow. Even in the mid 20<sup>th</sup> century, despite the progress made in the HPV virus research, scientists considered mechanical and chemical irritation of the skin as the primary cause of HPV-related lesions [25, 34]. Conventional wisdom of the time provided a wide variety of speculative causes such as repeated wetting of the hands, washing the hands in water in which eggs have been boiled, the killing of a toad (the slaughterer developing as many warts as the toad has spots) and the foam of the sea-shore [35]. In 1901, Heidingsfield will describe cauliflower-like raised lesions on the tongue of a prostitute. Heidingsfield established a correlation between the mucous lesions and repeated oral sex [36]. In 1907 Dr. Giuseppe Ciuffo (1877-1916) was the first to establish the viral origin of warts. To prove his initial theory Dr. Ciuffo successfully inoculated a wart extract that had been filtered through a pore with a size small enough to eliminate larger entities, such as bacteria and fungi, but not viral agents [37]. Nevertheless, Strauss was the first scientist to isolate the virus in crystal form in 1949 [38].

The findings regarding the viral origin of genital papillomatosis at the beginning of the 19<sup>th</sup> century were groundbreaking and paved the way for further discoveries. Experiments carried out on animals provided knowledge for the epidemiology and molecular biology of the disease. For many decades to come genital papillomatosis and common warts were considered to share a common origin. Scientists considered that all papillomatous lesions were caused by the same virus [33, 39-41]. In 1930, common warts, laryngeal papillomatosis as well as anogenital condylomas were associated to Human papillomavirus. In addition, Shope and Hurst first published scientific proof that related HPV infections to cancer. In 1934 they proved that members of the HPV-family had carcinogenic properties. Shope and Hurst used an animal model with rodents in order to prove their hypothesis [41]. During the upcoming decades scientific research documented the differentiation

process of infected human epithelial cells [42]. Owing to the development of new laboratory techniques and methods viral particles were isolated from human tissue and scrutinized. As a result, the entire viral genome of all members of the HPV-family was analyzed and decoded during the 1970s [43-45]. Certain HPV-subtypes are called high risk because persistent infection with these types lead to cancer of the oropharynx, larynx, vulva, vagina, cervix, penis, and anus. German professor Harald zur Hausen was first at illustrating the virus' carcinogenic potential. Apart from causing skin warts and other benign lesions human papillomaviridae were linked to malignancies, rendering them oncoviruses. Professor Hausen argued that HPV could lead to cervical cancer [46]. Through his work HPV-associated cervical cancer was established. HPV 16 and HPV 18 two high risk subtypes were recognized as potential culprits during the period 1983-1984 [47, 48]. Thus, the scientific basis for the development of an effective vaccine in 2006 was established. Professor zur Hausen was received the Nobel Prize in 2008 for his constructive and groundbreaking work around human papillomaviridae [49].

In 1978 Kreimer and his associates recognized the relationship between skin cancer and HPV infections [50]. Through his extensive analysis on HPV 16 and its causal relationship to head cancer Keimer revealed that these viruses were not tissue selective regarding their oncogenic capacity. Viral DNA strands in human skin cancer cells revealed the virus' clonicity. In addition, frequent oral sex and numerous sexual partners comprised critical risk factors for developing HPV-related oropharyngeal cancers [51, 52]. High-risk subtypes were recognized as etiologic agents and were linked to the pathogenesis of infiltrative cervical cancer [53]. Until 1989, 60 new subtypes were identified, as long as other already known subtypes [54, 55]. Moreover, scientific evidence that Head and Neck Squamous Cell Carcinoma (HNSCC) was also caused by subtypes of Human papillomaviridae was published in 1980 [56-58].

Scientific progress in regard to HPV-mediated infections was hindered by the absence of means to reproduce viral specimens. Contemporary laboratory techniques were insufficient for the *in vitro* replication of the virus. A lack of a cultivation means as well as the inability of horizontal transmission of the virus in animal models were two

factors that substantially delayed progress in the field. The development of novel techniques in the field of molecular biology contributed to the prompt identification of HPV types. In 2004, 30 previously unknown HPC subtypes were identified. All in all, HPV and its close connection to malignancies have established a model of viral carcinogenicity [59]. Nevertheless, evidence of HPV-related rectal adenocarcinoma from an Egyptian Mummy dated to 2400 BC, reveals that there is much more to be learned [60].

## ■ EPILOGUE

From the Hippocratic period in ancient Greece, HPV still poses great challenges to the medical community. A wide variety of HPV subtypes cause cervical cancer, while cutaneous lesions are common. Historical analysis of the origin and science surrounding Papillomaviridae continue.

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