

SPECIAL ARTICLE

Four historic legends in human papillomaviruses research

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Summary

Human papillomaviruses (HPVs) infection and HPVs-associated lesions, including skin warts in children and adults and cervical neoplasia in women, have been extensively studied since ancient years. In our article, we present briefly four major researchers from the HPVs pre-vaccination historic period: Hippokrates the Asclepiad, Domenico

Antonio Rigoni-Stern, George N. Papanicolaou and Harald zur Hausen.

Key words: HPVs, human papillomaviruses, Hippokrates, Papanicolaou, Rigoni-Stern, Harald zur Hausen

Introduction

HPVs-associated lesions, including skin warts, genital warts, squamous intraepithelial lesions (SILs) and cervical cancer, were first described in the 4th century BC by Hippokrates the Asclepiad from the island of Kos, referred as the 'Father of Medicine' [1-3]. Despite the fact that skin and genital warts have been considered infectious since this early period, the infectious cause of cervical cancer was only suspected in the 19th century AC by an Italian scientist from Asiago, Italy, the Surgeon Antonio Domenico Rigoni-Stern, referred as the 'Father of Cancer Epidemiology'. In 1928, a Greek scientist originated from the island of Euboea, Dr George N. Papanicolaou, referred as the 'Father of Exfoliative Cytology', observed precancerous HPVs-associated lesions in the vaginal smear collected from females, an observation which led him to develop the Pap smear test technique. It was not until the 1970s, approximately 40 years ago, that a role of HPVs in cervical cancer was postulated for the first time by Professor Harald zur Hausen, the 'Father of HPVs Virology'.

In our article, we present these four major researchers from the HPVs pre-vaccination historic

period (Hippokrates the Asclepiad, Domenico Antonio Rigoni-Stern, George N. Papanicolaou and Harald zur Hausen) and we cover briefly some of the historical aspects of their research and their contribution.

Hippokrates the Asclepiad

According to the Greek gynecologist of the 2nd century A.C. Soranos of Ephesus [4], Hippokrates the Asclepiad (Island of Kos, Greece, 460 B.C. - Larissa, Greece, 377 B.C.), referred as the 'Father of Medicine', was born on the 27th day of the month Agrianios, in the Greek island of Kos. His mother, named Fainareti, and his father, named Heraklides, claimed to be descended from Asclepius, who according to the Greek Mythology, was the God of Medicine and Healing. Hippokrates was the most outstanding ancient Greek Physician of the 4th century B.C., who personified the first rational, non-religious approach to medical practice, based on observation and reasoning [5]. His famous saying 'ὠφελέειν ἢ μὴ βλάπτειν' meaning 'to benefit, not to harm' has been depict-

ed as the most valuable principle in Medicine, while his Oath, Hippocratic Oath, represents the first code of practice, that still gives Medicine its ethical principles worldwide.

Hippocrates studied Medicine from his father Heraklides and he founded the reputed Hippocratic School of Medicine on the island of Kos in antagonism with the Medical School of Knidos. Hippocrates first recorded and described HPVs-associated infections, including skin warts, genital warts, SILs and cervical cancer [6]. For Hippocrates cervical cancer was so destructive that 'μὴ θεραπεύειν βέλτιον' [5], meaning 'it is better to be left uncured than treated'. Although Hippocrates was certainly not the first to discover cervical neoplasia, he referred to cervical lesions called 'ἕλκος' [4], meaning 'ulcer' that can potentially progress to cervical cancer pointing out the SILs progression to invasive cervical cancer. This knowledge referring to the physical history of HPVs infection in the cervix is apparent in Hippocrates' impressive description 'εἰ δὲ μὴ ἐμελεδάνθη, μηδὲ οἱ ἡ κάθαρσις ἐρράγν αὐτόματῃ, τὸ ἕλκος μέζον ἐποίησεν καὶ μὴ ἀνεῖσα ἐκινδύνευσεν εἰς τὸ καρκινωθῆναι τὰ ἔλκεα' [5], meaning 'if we do not take care of it, the catharsis will not be automatic, the ulcer will become bigger and if it does not regress, there is a risk for the carcinogenesis of the ulcers.

Domenico Antonio Rigoni-Stern

The Surgeon Domenico Antonio Rigoni-Stern (Asiago, Italy, 1810-Verona, Italy, 1855), one of the first Cancer Epidemiologists in the History of Medicine, was born on the 26th of June 1810 in the small town of Asiago in Italy [6]. He studied Medicine at the University of Padua, where he received his M.D., and after his specialization in Surgery in Vienna in Austria, he was appointed as a Provisional Surgeon of Verona and a Deputy Professor of Clinical Medicine at the University of Padua.

On the 23rd September 1842 he presented his research [7] to the IV Congress of the Italian Scientists in Verona, Italy. His findings, based on a series of mortality statistics of women dying of cancer in the city of Verona, pointed out that cervical cancer was related to sexual activity, being more common in married women and widows than in nuns and virgins. This was the first published epidemiological study, which using data from cancer registries of the city of Verona during the years 1760 to 1839, implicated an infectious cause for cervical cancer. His observation was an important

scientific step towards identifying the role of sexually-transmitted infections and was marked as the birth of Cancer Epidemiology [8]. Although other researchers [9] have questioned the value of his contribution, the suspicions of the Surgeon Domenico Antonio Rigoni-Stern, who was 'ahead of his time', were finally confirmed as sexually transmitted HPVs are now implicated etiologically in almost all cases of cervical carcinogenesis.

George N. Papanicolaou

Dr George N. Papanicolaou (Kyme, Island of Euboea, Greece, 1883- Miami, Florida, U.S.A., 1962), referred as the 'Father of Exfoliative Cytology', was undoubtedly an exceptional doctor, scientist and humanitarian of the modern History of Medicine - see a brief referral to his life in Mammias and Spandidos [10]. He was born on the 13th of May 1883 in Kyme, on the Greek island of Euboea, the same island as the ancient Physician Diocles of Karystos (340 B.C. - 260 B.C.), who according to Plinius was 'second only to Hippocrates' in fame for ancient Athenians [11]. Dr George N Papanicolaou studied Medicine at the University of Athens in Greece, where he received his M.D. in 1904 and in 1910 he received his Ph.D. from the University of Munich in Germany. In 1914 he joined the Cornell University Medical College's Department of Anatomy in the U.S.A., where he performed his scientific work for the rest of his life. His life has been characterized by his phrase: 'τό ἰδανικόν μου δέν εἶναι νά πλουτίσω, οὔτε νά ζήσω εὐτυχῆς ἀλλά νά εργασθῶ, νά δράσω, νά δημιουργήσω, νά κάμω κάτι τι ἀντάξιον ἑνός ἀνθρώπου ἠθικοῦ καὶ δυνατοῦ' [12], meaning 'my ideal is not to become rich, or to be happy, but to work, to act, to create, to do something worthy of an ethical and strong man'. His saying 'Ζῶ διὰ νά ὑπηρετήσω τὴν ζωὴν' [12], meaning 'I live to serve life' has been inscribed in his bronze statue situated at the entrance of his home island, Euboea close to the new Evripos Bridge spanning the 700 metres between Euboea and the mainland Greece [13].

After 1923, Dr George N. Papanicolaou extended the correlation of the vaginal smear cytology with the ovarian cycle in pregnant and non-pregnant women and he managed to include specimens from patients with endocrine and genitourinary diseases. In continuing his work on human specimens with cervical cancer, he discovered that women with cervical cancer exhibited 'abnormal cells, with enlarged, deformed or hyperchromatic nuclei.' He termed it as 'one of the

most thrilling experiences in my scientific career' [12]. In January 1928, he presented his findings, entitled as 'New Cancer Diagnosis' at the Third Race Betterment Conference in Battle Creek, Michigan, where he introduced his low-cost, easily performed screening test for early detection of cancerous and precancerous cells [14]. However, this potential medical breakthrough was initially met with skepticism and resistance from the scientific community at that time and his technique was initially considered as an unnecessary addition to the existing diagnostic methods for cervical cancer [12].

Almost 10 years later, in 1939, at the encouragement of the gynaecologist Dr Herbert Traut, Dr George N. Papanicolaou continued his work in this field and on the 11th of March 1941, Papanicolaou and Traut published their findings in their paper entitled 'The diagnostic value of vaginal smears in carcinoma of the uterus' [15]. At this time the Pap smear test technique [16] won acceptance and soon became widely accepted as a routine screening methodology, worldwide. The Pap smear test as a cytological HPV-test detecting early HPV-associated SILs is a unique precancerous screening test yet developed in the entire history of Medicine. This test is credited with reducing cervical cancer mortality by more than 70% in countries where PAP smear test was included in the national prevention strategies against cervical cancer. Although Dr George N. Papanicolaou ignored the viral existence of HPVs, his intervention was definitely a more than significant step in the field of HPVs Virology.

Harald zur Hausen

Professor Harald zur Hausen (Gelsenkirchen-Buer, Germany, 1936-), born on the 11th of March 1936 in Gelsenkirchen-Buer in Germany, studied Medicine at the Universities of Bonn, Hamburg and Düsseldorf and received his M.D. in 1960 [17]. In 1966 he went to the U.S.A. to the Children's Hospital of Philadelphia, where he joined the Laboratory of Dr Werner Henle and Dr Gertrude Henle and in 1968 he was appointed as Assistant Professor of Virology at the University of Pennsylvania. In 1969, he returned to Germany and after a period of 3 years as a senior scientist at the Institute of Virology of the University of Würzburg, he was appointed in 1972, at the age of 36, as Chairman and Professor of Virology at the University of Erlangen-Nürnberg in Bavaria. In 1977, he moved to a similar position at the Uni-

versity of Freiburg and from 1983, until his retirement in 2003, he was appointed as a Scientific Director of the Deutsches Krebsforschungszentrum (German Cancer Research Center) in Heidelberg. On the 6th of October 2008, Professor Harald zur Hausen received the Nobel Prize in Physiology or Medicine 'for his discovery of HPVs causing cervical cancer', a discovery that proved the principal role of HPVs in cervical cancer and led to the development of the current vaccines against HPVs.

Professor Harald zur Hausen's first experiments trying to establish an aetiological relationship between HPVs and cervical cancer were initiated in 1972 [18]. As his research group failed to find genetic DNA sequences for herpes simplex virus type 2 in cervical cancer biopsies, he went against the dogma of that time that herpes simplex viruses (HSVs) are associated with cervical carcinogenesis. This false dogma implicating HSVs had gained a catholic scientific acceptance since the end of 1960s and had been supported by gynaecologists for more than two decades. Professor Harald zur Hausen's principal observation that HPVs are not a single virus but many with a major heterogeneity led his research group to be the first, during the late 1970s, to isolate HPV 6 from genital wart biopsies, HPV 11 [19], HPV 16 [20] and HPV 18 [21] from cervical cancer biopsies and to hypothesize that cervical cancer is mainly caused by HPVs. This hypothesis achieving a major breakthrough in the field of Virology and a huge progress in women's health in the coming years, was totally new and the scientific community at that time was not enthusiastic enough to accept the viral etiology of cervical cancer. Moreover, in 1984, pharmaceutical companies turned down Professor Harald zur Hausen's request to work on developing a vaccine against HPVs, as they 'did not believe that this would be profitable and there were more urgent problems to be solved' [22].

However, by the beginning of 1990s, the use of HPVs DNA testing in an excessive number of epidemiological and molecular studies, aided greatly by Professor Harald zur Hausen's policy of rapid distributing upon request the HPVs DNA genomes that his Laboratory had cloned, confirmed that HPVs are indeed the main causative agent for cervical cancer [23]. After the beginning of the vaccination period against HPVs [24], HPVs are well established as the viruses of Professor Harald zur Hausen, a great pioneer of modern Virology in the entire History of Medicine, who can be undoubtedly known as the 'Father of HPVs Virology'.

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