

Condylomata, HPV and Cervical Cancer

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MILESTONES

Meisels A, Fortin R: **Condylomatous lesions of the cervix and vagina. I. Cytologic pattern.** *Acta Cytologica* 1976, 20:505-509,

Meisels A, Fortin R, Roy M: **Condylomatous lesions of the cervix. II. Cytologic, colposcopic and histopathologic study.** *Acta Cytologica* 1977, 21:379-390



Alexander Meisels

These two cited papers are landmark publications in the history of investigative pathology for several reasons, the most important of which is the profound and lasting impact they have had on women's health. Today, we work in an era of biomedical research where there is a growing emphasis on "translational research." This

term usually means advancing clinical practice through the application of knowledge generated in the basic research laboratory. The studies of Meisels and colleagues^{1, 2} certainly had an immediate clinical impact, but their work is also an excellent example of translational research vectored in the reverse direction: observations made in the clinic stimulated basic research in the molecular genetics and biology of human papilloma viruses that advanced the field and continues to the present day. The investigations of Meisels employed an approach and a set of technologies, which by today's standards would be considered rather simple. Their findings yielded fundamental insight into an important human cancer.

Compared to the numerous and often sophisticated tests that have been devised to detect the presence of a cancer, the simple technique for examining exfoliated cells in vaginal secretions described by the anatomist George Papanicolaou³ has no peer when measured in terms of a public health impact. Before the Pap smear came into widespread use in the United States, cervical cancer was the leading cause of death from cancer in women, but it now ranks eighth. This dramatic fall in mortality rate reflects the early and effective treatment of asymptomatic patients whose vaginal cytology showed the presence of cancer cells, or cells indicative of a pre-malignant lesion. Although the mortality rate from cervical cancer is now relatively low, approximately one million cases of precancerous conditions of the cervix are detected annually by Pap smears in the United States. In countries such as Viet Nam, where

nationwide cytology screening does not occur, cervical cancer is the leading cause of death from cancer in women.

The investigations by Meisels and colleagues^{1,2} were milestone contributions because they established that papilloma virus infection of the cells that line the uterine cervix was very common and that it was a high risk factor for the subsequent development of cervical cancer. At the time these studies were published, it was already known that a papilloma virus was the etiological agent of *Condyloma acuminatum*, a sexually transmitted disease that, because of the appearance of the lesions, is commonly referred to as venereal warts. These are benign squamous cell tumors that occur on the external genitals and the perineal skin in females and males. Instances of malignant transformation of these lesions had been reported in the literature, but were rare. Epidemiologic studies had established that the risk factors for developing venereal warts were the same as the risk factors for developing cervical cancer. These included sexual promiscuity and the initiation of sexual activity at an early age. A characteristic microscopic feature of venereal warts is the presence of a striking paranuclear halo in some of the squamous epithelial cells. Cytologists had occasionally observed cells with paranuclear halos in vaginal smears from women who did not have a history of venereal warts, but these cells received little comment and their significance was unknown. The first published description of halo cells was in 1949 by J. Ernest Ayre, a pathologist at the Royal Victoria Hospital in Montreal, who considered them to be "precancerous cells"⁴. The conspicuous halo present in these cells prompted Koss and Durfee in a 1956 paper⁵ to designate them as koilocytes (koilos, the Greek word for hollow or cavity). Ayre⁶ was the first to mention in the literature that halo cells might be a manifestation of a viral infection. Meisels' investigations¹ established that the koilocytes present in vaginal secretions had cytological features in common with the halo cells present in venereal warts. In a very systematic study of otherwise normal women whose vaginal smears contained halo cells, Meisels and

colleagues² detected focal alterations of the cervical surface which were rather inconspicuous and easily missed on routine clinical examination. Biopsies of these lesions revealed the presence of halo cells and other histological features indicating that they were flat or inverted condylomata. In contrast to the conspicuous papillary excrescences of condyloma acuminatum of the external genitals and perineal skin, Meisels discovered that condyloma of the cervix were usually tiny, flat non-specific lesions that could easily be confused with other types of epithelial lesions. Once Meisels established the cytological criteria for condyloma¹, it soon became clear that most vaginal smears previously diagnosed as cervical dysplasia were actually cases of cervical condyloma.

In discussing their findings Meisels and colleagues² proposed that cervical condyloma might be an early step in the natural history of cervical neoplasia. The age of peak incidence of cervical condylomas in their study was 19 years, which is a significantly younger age than the peak incidence for carcinoma of the cervix. Since cervical condylomata eventually disappear, they proposed that the virus becomes latent, but that "later in life if host factors become favorable (lower immunity against the virus, repeated local trauma, infections and infestations of the cervix) the virus, probably now integrated in the host genome, activates the mechanisms of carcinogenesis." The essence of their proposal remains valid today.

During the decades that followed publication of these milestone articles, the field of human papilloma virus (HPV) research has grown tremendously. More than 70 different types of HPV have been identified from clinical specimens and it is clear that a large number of subtypes and variants exist for each type of HPV. There is now an abundance of evidence that links HPV to cervical cancer and its precursor conditions. HPV DNA is detected in 85% of cervical cancers and 90% of cervical condylomata. Distinct HPV types ("high risk" types) are associated with cervical cancer. It is known that in condylomata, HPV exists in an episomal (non-integrated) form but in cervical cancer the HPV is integrated into the host genome. The site in the human DNA where HPV integration occurs is random, but the site where the viral DNA is interrupted during integration is selective and results in the over-expression of two viral proteins that block the action of two host-cell proteins that are key regulators of the cell cycle. Currently, clinical trials are testing the efficacy of vaccines containing peptides from high-risk types of HPV as an immunotherapeutic strategy to prevent HPV-associated genital cancers.

Collectively, these are impressive advances in a field that is rapidly approaching a detailed molecular understanding of an important human cancer. The studies of Meisels and colleagues provided a tremendous impetus to this field. The simple methodology developed by Papanicolaou set the stage. It is ironic that vaginal cytology, unquestionably the greatest success story in the field of human cancer, was initially met with such deep skepticism and strong resistance from within the discipline of pathology. Fortunately, the early practitioners of cytology persisted.

References

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