High Prevalence of Cervical Dysplasia in Female Consorts of Men with Genital Warts

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Altogether 51 regular female consorts of men attending a venereal disease clinic for genital warts were examined using colposcopy, vaginal cytology and—when needed—surgical biopsy. Abnormal cytological smears were found in 18 out of 49 consorts (37%), which should be compared with 8 out of 124 (6%) matched female controls from a family planning clinic ($p<0.001$). Possibly premalignant lesions, i.e. atypical condylomata and/or frank dysplasia, were found in 14 (27%) out of 51 consorts. The prevalence of abnormal smears or biopsy-proven dysplasia was approximately the same in consorts with and without external warts. These findings call for close attention to the risk of development of cervical dysplasia in female consorts of men with genital warts. *Key words: Sexually transmitted disease; Human papilloma virus infection; Colposcopy; Cytology.* (Received February 19, 1987.)

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Sexual behaviour, especially features associated with a high risk of sexually transmitted diseases (STD), have long been identified as important risk factors in the epidemiology of cervical cancer and its precursors (1).

During the sixties and early seventies, research mainly focused on herpes simplex viruses (2), without any conclusive results. Later evidence suggests Human Papilloma Viruses (HPV) as an important etiological agent in cervical carcinogenesis (3).

Venereal transmission of HPV causing genital warts is documented in both men and women (4). In this study, the risk of development of subclinical HPV infection and cervical dysplasia in female sexual consorts of men with genital warts is presented.

PATIENTS AND METHODS

Patients

During the period of February to August, 1984, 154 men with genital warts attended the Venereal Disease (VD) clinic at the Department of Dermatology, Sahlgren's Hospital, Göteborg. All were interviewed about their recent sexual contacts. Regular female consorts (at least 2 months) were recommended to come for examination if they were not already under treatment for condylomata. Thus, fifty-one women, 16–49 years old (mean age 24 years), recently exposed to genital wart infection were included in the study.

At the patient's first visit to the VD clinic, a general history including data about contraceptive practice, earlier STD and casual sexual contacts, was taken. Routine examinations, including a serological test for syphilis, stained smears from the urethra and cervix, a wet smear from vaginal secretion and culture from the urethra and cervix for gonorrhoea and chlamydia, were performed. Condylomata were carefully looked for in the vulva, around the anus and in the vagina. Smears for routine cytology from the upper vaginal vaults, the portio and the endocervix were obtained with standard techniques.

All 51 patients were seen 1–3 months later at the colposcopy clinic of the Department of Gynecology. Those patients who had either an abormal vaginal smear or an abnormal colposcopic lesion were subjected to biospy (from the cervical transformation zone, and colposcopic lesions in the vagina) and endocervical curettage.

Controls

During the same period, cytological smears were taken from 639 sexually active women of the same ages who consulted the Family Planning Clinic at the Department of Gynecology, Sahlgren's Hospital. From these, 2 or 3 women were selected as controls for each of the patients, matched as closely as possible for age, parity, contraceptive practice and date of examination. The final group consisted of 124 women aged 16-41 with a mean age of 23 years.

Colposcopy procedure and classification

The cervix and the vagina were carefully examined using a Zeiss colposcope before and after washing with 3% aqueous acetic acid. The findings were classified as follows:

Normal

Acetowhite: All cervices that were distinctly white after the application of acetic acid but had no other unusual features.

Warty atypia: Cervices or vaginal fornices with either frank exophytic condylomata or papillary projections of acetowhite epithelium or rough-surfaced, "brainlike", shiny white epithelium which had a speckled appearance after application of Lugol's iodine but showed no pathological capillary pattern.

Mosaicism or punctation: Cervices with dull acetowhite epithelium containing the capillary patterns suggestive of dysplasia and negative staining with Lugol's iodine.

Mixed lesion: All cervices which had the features of both warty atypia and dysplasia (mosaicism or punctation).

Cytological procedures and classification

Papanicolau-stained smears were re-examined by the same cytologist. Control smears and smears from papilloma virus-exposed patients were mixed and their identity was not known to the examiner. Individual records were established, listing all nuclear and cellular changes (i.e. orangophili, amphophili of the cytoplasm, chromatin smudging, bi- or multinucleation, individual cell keratosis, nuclear atypia). Two or more typical koilocytes were required for the diagnosis of koilocytosis.

For the purpose of this paper, the following groups were established:

Normal: Including reactive cell aberrations.

Koilocytosis: Implicating the koilocytic cell according to Reid et al. (3, 5) as the only single diagnostic criterion for HPV-virus infection.

Koilocytosis and dysplasia: Smears with foci of both koilocytic cells and separate cell groups with atypia of dysplastic type only.

Dysplasia: According to standard definitions.

Histopathological procedures and classification

Fixation in 10% neutral formalin was used. Biopsy and curettage specimens were totally embedded in paraffin and sectioned in the normal way. At least four sections from each block were taken and stained, usually according to van Gieson. All slides were examined by the same pathologist. A record of all nuclear, cellular and structural changes was written for each patient.

For the purpose of this paper, histopathological findings were classified in the following groups:

Normal or unspecific: Including inflammatory and reactive changes.

Koilocytosis: This term was used for the classical cellular changes in HPV-infections, described by Reid et al. (3.5).

Koilocytosis with atypia: When nuclear atypia in koilocytosis were more advanced than according to the definition of a koilocyte corresponding to "atypical condyloma".

Koilocytosis and dysplasia: When koilocytosis and frank dysplasia were seen in different places.

Dysplasia: Mild, moderate or severe (=carcinoma in situ) according to standard definitions.

Statistical procedures

Standard procedures for calculation of means and variations were used. Comparison between groups was made by the chi square method using Yate's correction (6). $\rightarrow$: p-values less than 0.05 were considered significant.

RESULTS

In 18 (35%) of the 51 examined female consorts, obviously visible condylomata were registered.

Colposcopy disclosed abnormal findings in 42 of the 51 women examined. Seventeen had colposcopic signs of HPV infection, i.e. warty or mixed lesions, thirteen women had mosaicism and/or punctation suggestive of cervical dysplasia alone and in 11 women nonspecific acetowhite lesions were found. Nine patients had colposcopically normal cervices.

Cytology (Table I and II)

Abnormal findings, suggesting dysplasia and/or HPV infection, were found in 18 out of 49 patients in whom the original smears were available for revision, compared to 8 out of 124 controls, i.e. 37 vs. 6% ($p<0.001$). Abnormal smears were found in 7 out of 16 (44%) women with obvious genital warts and in 11 out of 33 (33%) with no visible warts. This difference in incidence, 44 vs. 33%, is not significant.

Histopathological diagnoses (Table III)

In those 43 patients who were biopsied premalignant lesions (i.e. atypical condylomata or dysplasia) were seen in 7 (41%) of 17 patients with obvious genital warts and in 7 (27%) of 26 patients without visible warts. This difference is not significant. Cervical HPV infection was demonstrated in 16 (37%) of 43 patients.

Colposcopy vs. histopathology (Table IV)

Significant atypia or dysplasia was demonstrated histopathologically in 4 (16%) out of 25 women in whom colposcopy suggested non-dysplastic lesions (although none had a completely normal cervix). In 9 (47%) out of 19 cervices where colposcopy suggested a

Table I. *Cytological findings in 49 female consorts of men with penile condylomata and 124 women from the Family Planning Clinic*

Cytological diagnosis	Patients $n=49$	Controls $n=124$
Normal	31 (63%)	116 (94%)
Koilocytosis	7 (14%)	5 (4%)
Koilocytosis and dysplasia	8 (16%)	0 (0%)
Dysplasia	3 (6%)	3 (2%)

Table II. *Cytological findings in 49 female consorts of men with genital warts*

Cytological diagnosis	Patients with obvious genital warts $n=16$	Patients without visible condylomata $n=33$
Normal	9 (56%)	22 (67%)
Koilocytosis	3 (19%)	4 (12%)
Koilocytosis and dysplasia	3 (19%)	5 (15%)
Dysplasia	1 (6%)	2 (6%)

dysplastic lesion, histopathology revealed only non-specific inflammation or a non-dysplastic koilocytic lesion.

Cytology vs. histopathology (Table V)

Significant cervical dysplasia was found in 5 (15%) out of 32 women in whom cytology was normal or suggested non-dysplastic koilocytosis. On the other hand, only in one case there was normal histopathology found, when cytology suggested dysplasia.

Table III. *Histopathological findings (portio cervix) in 43 female consorts of men with genital warts*

Histopathological diagnosis	Patients with obvious genital warts $n=17$	Patients without visible warts $n=26$	Total $n=43$
Normal or unspecific inflammation	8	16	24 (56%)
Koilocytosis	2	3	5 (12%)
Koilocytosis with atypia	1	2	3 (7%)
Koilocytosis and dysplasia	4	4	8 (18%)
Dysplasia	2	1	3 (7%)

Table IV. *Colposcopic findings and histopathological diagnosis in cervical biopsies of 43 female consorts of men with genital warts*

Colposcopic findings	Histopathological diagnosis				
	Normal or unspecific	Koilocytosis	Koilocytosis with marked atypia	Koilocytosis and dysplasia	Dysplasia
Normal	1	–	–	–	–
Acetowhite, unspec.	10	1	–	–	–
Warty (HPV)	7	1	1	2	1
Mosaicism or punctation (dysplasia)	5	3	1	3	2
Mixed lesion (HPV + dysplasia)	1	–	1	3	–

Table V. *Cytological and histopathological diagnoses in cervical biopsies of 42 female consorts of men with genital warts*

Cytological diagnosis	Histopathological diagnosis				
	Normal or unspecific	Koilocytosis	Koilocytosis with marked atypia	Koilocytosis and dysplasia	Dysplasia
Normal	20	3	1	1	1
Koilocytosis	4	–	–	2	–
Koilocytosis and dysplasia	1	1	2	3	–
Dysplasia	–	–	–	1	2

Concomitant STD

Seven (14%) out of 51 patients had positive cultures for chlamydia, one (2%) for gonorrhoea and 4 (8%) had signs of bacterial vaginosis. Three patients had a positive history of genital herpes simplex virus infection. All these STDs were equally distributed between patients with and without cervical dysplasia.

DISCUSSION

The study has revealed a high incidence of HPV infection in female consorts of men with genital warts.

The prevalence of abnormal smears was 7 times higher in the studied women exposed to HPV infection than in the control group. Unfortunately, it was not possible to match for age of first sexual contact and number of sexual partners, although matching was done for other indices of sexual practice such as duration of contraception and pregnancies. Furthermore, the studied patients did not have a significantly higher prevalence of chlamydia or other STD than the average sexually active female population in Sweden (7). Campion et al. (8) found cervical dysplasia in 9 out of 25 (36%) female partners of men with penile condylomata and in no female consorts of men with non-specific urethritis. The sexual behaviour of these women and their male consorts (as judged by age of first intercourse, number of partners or prevalence of other STD) did not differ between those with cervical dysplasia and those without.

The present and the quoted findings thus support the view that HPV plays a significant role in the pathogenesis of cervical neoplasia. HPV types 6, 11, 16 and 18 are associated with genital warts. HPV type 16 and, to a lesser extent, type 18 appear to be associated with cervical neoplasia and have been found in invasive cervical cancers (9).

The prevalence of significant cervical dysplasia of 35% in patients with obvious warts and 20% in patients without visible condylomata is compatible with the rate of cervical dysplasia (30%) in women with vulvar condylomata reported by Walker et al. (10).

HPV-associated lesions, as well as dysplasia, were suggested colposcopically in some cases that could not be confirmed by histopathology. Apart from the uncertainty of colposcopy, this discrepancy could also be explained by the fact that there is not complete correlation between immunological and histopathological demonstration of HPV-infections (9). Furthermore, microbiological studies using DNA hybridization indicate the presence of HPV without morphological signs of HPV-infections (9, 11). The histopathologically verified cases of koilocytes must therefore be regarded as the minimum incidence of HPV infection in the study.

It is obvious that both colposcopy and cytology are needed to discover all cases of dysplasia and that nonsignificant acetowhite lesions should be biopsied if the cytology is abnormal. Conversely, benign or inflammatory smears should be considered significant if colposcopy reveals a mosaicism or a mixed lesion in women exposed to HPV. Other authors (12) have suggested that the colposcopic pattern is of prognostic value, indicating progression to dysplasia in cases of HPV-infection and, in fact, two women in this series, with only nonspecific inflammatory or non atypical koilocytotic lesions in the first biopsy developed severe dysplasia within a year.

In our opinion, these results call for close surveillance of women exposed to HPV infection, not only with regard to prevention of spread and reinfection but also for prevention of future cervical and possibly multifocal anogenital squamous neoplasia in these women. This surveillance should include repeated cytology and, if possible, colposcopy. In the future, the typing of HPV may be a useful tool for selecting those women who

need the closest surveillance with respect to the risk of developing lower genital tract carcinomas.

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