

## Human Papilloma Virus Infection (Condyloma) of the Uterine Cervix in Japanese Women<sup>\*</sup>

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### ABSTRACT

Fifty-seven cases previously diagnosed as either dysplasia or carcinoma in-situ by three Japanese medical centers were reviewed and reclassified as either condyloma, CIN I, II, III or squamous metaplasia. Of 46 cases previously diagnosed as mild or moderate dysplasia (CIN I-CIN II) 13 were reclassified as condylomata. Immunoperoxidase localization of human papilloma virus antigens was negative in 21 cases of CIN and positive in 3 of 5 cases classified as condylomata. The prevalence of human papilloma virus infection in these Japanese women appears to be similar to that reported in other countries including Western Europe and the United States.

### INTRODUCTION

In recent years it has become recognized that a high percentage of abnormal Pap smears in young women are the result of human papilloma virus infection (condyloma) of the lower female genital tract<sup>6)</sup>. It has also become clear that condylomata may coexist with cervical intra-epithelial neoplasia (CIN) in approximately 25% of cases, and that CIN and condylomata may coexist in continuity in the same epithelium<sup>6)</sup>. As CIN is a recognized cancer precursor it has been suggested that the human papilloma virus may be a significant oncogen in the lower female genital tract<sup>7)</sup>. Although the incidence and prevalence of condyloma of the cervix have been studied extensively in the western countries<sup>6)</sup>, the incidence of cervical condyloma in other countries, including Japan is unclear. It is important to determine whether flat condylomata comprise a significant proportion of cervical lesions in Japanese women.

Although histological criteria alone are useful

for distinguishing condylomata from CIN, objective techniques for localizing human papilloma virus virions or antigens within infected cells are available and provide an objective basis for classifying cytologically atypical squamous lesions of the cervix, vagina and vulva. Cervical condylomata are generally polyploid<sup>4)</sup> and express viral antigens in approximately 50% of the cases<sup>3)</sup>. Although papilloma-virus antigens have been described in cervical dysplasias<sup>5)</sup>, there is no evidence that they are present in neoplastic epithelium with any regularity<sup>1)</sup>.

The present study was designed to assess the prevalence of condyloma in a series of lesions from Japanese women previously diagnosed as CIN and to corroborate the histological observations with immunoperoxidase localization of human papilloma virus.

### MATERIALS AND METHODS

Fifty-seven cases previously diagnosed as CIN (dysplasia and carcinoma in-situ) were obtained

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from Hiroshima University, Kyusyu University and the Osaka Cancer Research Center. The lesions were reviewed and classified according to the following scheme: 1) Flat condylomata. These lesions were characterized by basal or parabasal cell hyperplasia with minimal nuclear pleomorphism or atypism, an absence of abnormal mitotic figures, the presence of an orderly sequence of maturation and characteristic koilocytosis of the intermediate and/or superficial cells (Figure 1). 2) CIN. CIN was diagnosed on the basis of nuclear pleomorphism and hyperchromatism, and/or the presence of abnormal mitotic figures in an immature cell population. The grading of CIN I, CIN II or CIN III was used depending upon whether the undifferentiated neoplastic cells occupied the lower one-third, two-thirds or the entire thickness of the epithelium (Figures 2, 3).

Twenty-six of these cases were stained by immunohistochemistry, using the peroxidase/anti-peroxidase technique outlined previously<sup>9)</sup> using an antiserum to DODECYL-disrupted HPV virions from human plantar warts. The antiserum was kindly provided by Dr. Franklin Pass.

### RESULTS

Of the 57 cases we reviewed 11 had been diagnosed as CIN III (carcinoma in-situ or severe dysplasia) 27 as CIN II (moderate dysplasia) and 19 as CIN I (mild dysplasia). Using the aforementioned criteria, we diagnosed 10 as these cases as CIN III, 14 as CIN

II, 5 as CIN I and 13 as condyloma. Fifteen cases were reclassified as non-specific atypias, including squamous metaplasia or repair. Hence, of 46 cases initially diagnosed as mild and moderate dysplasia, 13 were reclassified as flat condylomata (Table 1).

Twenty-six of the cases were studied immunohistochemically, including 9 cases of CIN III, 9 of CIN II, 3 of CIN I and 5 of condyloma. Of the 21 cases we classified as CIN none were positive for HPV, whereas 3 of 5 cases we classified as condylomata were immunoperoxidase-positive (Table 2). Positive staining, as noted by previous investigators, was localized almost exclusively to the nuclei of the koilocytic superficial and intermediate cells (Figure 1).

### DISCUSSION

On the basis of this study it would appear that in Japan, as in the western countries for which data is available, cervical condylomata comprise a high percentage of cervical lesions as well as a high percentage of those lesions previously diagnosed as low grade CIN (CIN I and CIN II). Excluding non-specific atypias, the percentage of mild dysplasias reclassified as condylomata (60%) parallels the experience of other investigators<sup>6)</sup>. Thirty-three percent of the lesions originally classified as moderate dysplasia were re-classified as condylomata, emphasizing the histologic variability of human papilloma virus infection. The high incidence of misdiagnosis appears to be due primarily to the fact that the degree and extent of koilo-

**Table 1.** Classification of cervical Lesions

		Diagnosis on Review					Total
		CIN III	CIN II	CIN I	Condyloma	Non-specific	
Original	CIN III	8	3				11
Diagnosis	CIN II	2	9	3	7	6	27
	CIN I		2	2	6	9	19
		10	14	5	13	15	57

**Table 2.** Results of immunoperoxidase localization of papilloma virus antigens

	Lesions			
	CIN III	CIN II	CIN I	Condyloma
HPV Positive	0	0	0	3
Number Examined	9	9	3	5

cytosis and parabasal cell hyperplasia may vary from lesion to lesion and the fact that epithelium infected by the papilloma virus may on occasion contain minimal maturation and may mimic high grade CIN. The distinction between an infectious and a neoplastic process may generally be made histologically by careful attention to the basal and parabasal cell layers, which should contain minimal cytologic atypia in wart virus infection and significant cytological pleomorphism in all regions of the epithelium in CIN (Figure 2, 3). These distinctions may be confirmed by objective techniques such as immunoperoxidase localization of human papilloma virus antigens and DNA microspectrophotometry<sup>4)</sup>.

It is clear from other studies that polyploid cervical lesions generally regress and do not progress to higher grades of CIN or invasive carcinoma<sup>4)</sup>. From our current experience it seems probable that many of these polyploid lesions are in fact condylomata. On the other hand koilocytosis appears to be a nonspecific epithelial change sometimes found in CIN lesions and cannot be used as the sole differential diagnostic criterion to distinguish between CIN and condyloma.

The exact role played by papilloma virus in the genesis of invasive carcinoma of the cervix is unclear. It is apparent however that a significant percentage of CIN lesions coexist with condylomata, suggesting that a subset of intraepithelial neoplasms is directly related to papilloma virus infection<sup>2,6)</sup>. Whether these lesions have a greater risk of progressing to invasion than those not associated with papilloma virus infection is unknown. It is of interest however,

that those patients in whom CIN coexists with condylomata are younger in the aggregate than are those in whom it does not, suggesting that the viral infection may play a role in the natural history of this disease<sup>2,3)</sup>.

## REFERENCES

1. **Crum, C. P., Braun, L. A., Shah, K. V., Fu, Y-S., Levine, R. U., Fenoglio, C. M., Richart, R. M. and Townsend, D. E.** 1982. Vulvar intraepithelial neoplasia: correlation of nuclear DNA content and the presence of human papilloma virus (HPV) structural antigen. *Cancer* **49** : 468-471.
2. **Crum, C. P., Egawa, K., Barron, B., Fenoglio, C. M., Levine, R. U. and Richart, R. M.** Human papillomavirus infection (condyloma) of the cervix and cervical intraepithelial neoplasia: a histopathologic and statistical analysis. Submitted *Gynecol. Oncol.*
3. **Ferenczy, A., Braun, L. and Shah, K. V.** 1981. Human papillomavirus (HPV) in condylomatous lesions of cervix: a comparative ultrastructural and immunohistochemical study. *Am. J. Surg. Pathol.* **5** : 661-670.
4. **Fu, Y-S., Reagan, J. W. and Richart, R. M.** 1981. Definition of precursors. *Gynecol. Oncol.* **12**(Suppl. 1) : 220-231.
5. **Kurman, R. J., Shah, K. V., Lancaster, W. D. and Jenson, A. B.** 1981. Immunoperoxidase localization of papillomavirus antigens in cervical dysplasias and vulvar condylomas. *Am. J. Obstet. Gynecol.* **140** : 931-935.
6. **Meisels, A. and Morin, C.** 1981. Human papillomavirus and cancer of the uterine cervix. *Gynecol. Oncol.* **12** (Suppl. 1) : 111-123.
7. **zur Hausen, H.** 1977 Human papillomavirus and their possible role in squamous cell carcinoma. *Curr. Top. Microbiol. Immunol.* **78** : 1-30.

**Fig. 1a.** A characteristic flat condyloma of the cervix contains minimal parabasal cell pleomorphism, orderly maturation and koilocytosis, often with multinucleation.

**Fig. 1b.** An immunoperoxidase stain with antiserum to human papilloma virus illustrates reaction product in the nuclei of the koilocytic cells. (Arrows)

**Fig. 2.** CIN II. Note that there is basal pleomorphism and hyperchromatism with maturation of the upper two-thirds of the epithelium.

**Fig. 3.** CIN III. This lesion contains a near full-thickness population of neoplastic immature cells.

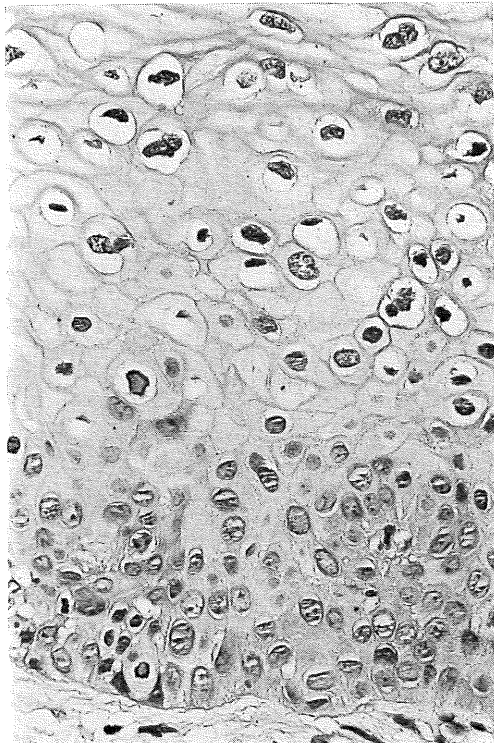


Fig. 1a

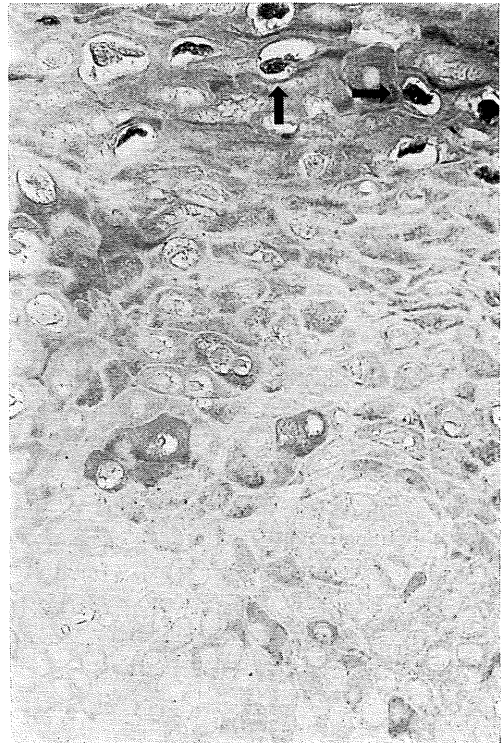


Fig. 1b

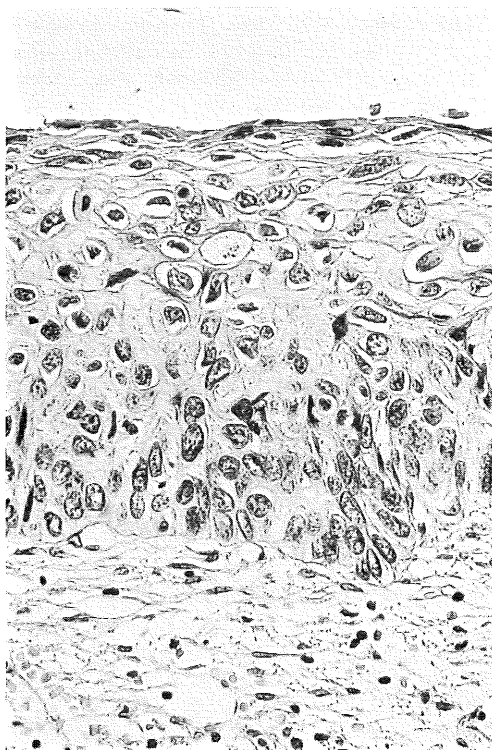


Fig. 2

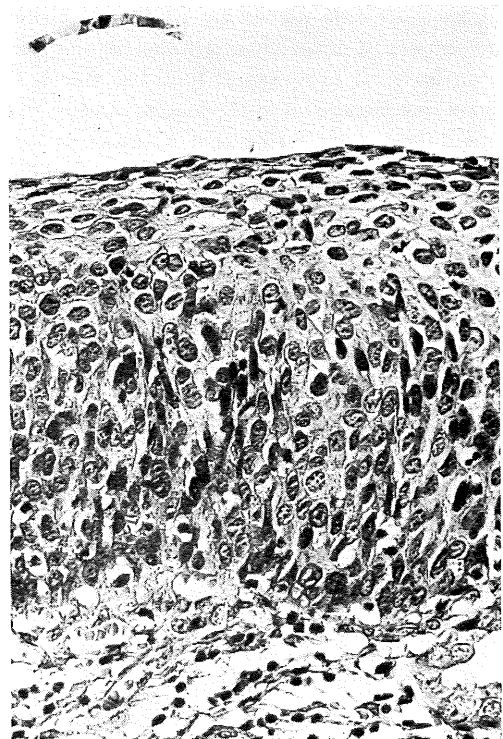


Fig. 3