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# Screening for cervical intraepithelial neoplasia and cancer in the Sheffield STD clinic

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SUMMARY I undertook a prospective study of the incidence of histologically confirmed cervical intraepithelial neoplasia (CIN) and cancer in women attending a sexually transmitted disease (STD) clinic, and correlated the findings to cervical cytology reports, age, and history of STD of the affected women.

Of 2017 women screened, 75 (3·7%) had dyskaryotic cervical smears. Colposcopically directed biopsy tests gave an overall detection rate of 0·55% for CIN3, which was similar to the national average.[29] The false negative rate was 2·9% and cytology tests alone underestimated the degree of pathological change in 12 (30%) of 40 women with mild dyskaryosis. Women under 20 years old made up 43% of those with CIN1 and 38% of those with CIN2. The detection rate of CIN3 was 0·65% for women aged 15-34, which was higher than the national average and suggested earlier onset of CIN3 in our clinic population. There was a high association between genital warts and cervical precancer.

This preliminary study confirms the need for routine non-selective screening of women attending STD clinics by cervical cytology tests, colposcopic examination, and biopsy tests where indicated.

## Introduction

Since Rigoni-Stern in 1842 first noted the rarity of cervical cancer in certain orders of nuns,[1] many epidemiological studies have associated early sexual activity, promiscuity, and low socioeconomic status with cervical precancer (cervical intraepithelial neoplasia (CIN)) and cancer.[2-5] High rates (1-9%) of cancer and precancer have been noted in prostitutes,[6] prisoners,[7 8] and women attending clinics for sexually transmitted disease (STD).[9]

As there seems to be a large sexually transmitted component in the origin of CIN, it is not surprising that a number of sexually transmitted agents have been studied by epidemiologists to find a causative agent.[3 10 11] Thus, human papilloma virus (wart virus (HPV)),[12 13] herpes simplex virus type II (HSV II),[10 11 14] *Chlamydia trachomatis*,[15 16] and *Trichomonas vaginalis*[17] have all been studied, as has the role of spermatozoa.[18] It is surprising that there is a recent dearth of published reports on the subject of CIN and cancer of the cervix in STD clinics, when all evidence strongly suggests a venereal aetiology.

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I undertook a prospective study of women attending an STD clinic to determine: a) the incidence of CIN and cancer, b) correlation of exfoliative cervical cytology with histology, and c) the age and STD profile of affected women.

## Patients and methods

Women attending this department of genitourinary medicine from January 1982 to June 1983 inclusive had a cervical cytological examination: at first attendance if they were over 21 and had not had a cytological examination in the past five years (n = 912); at first presentation with genital wart virus infection (HPV) (n = 585); at first presentation with genital herpes (HSV) and yearly thereafter (n = 400); if they had previously had abnormal cytology, cervical appearances suggesting neoplastic change, warts or polyps; and at the discretion of the examining physician if he or she considered it to be necessary irrespective of the above criteria (n = 120).

A total of 102 women who had had cytological examination underwent colposcopy. Of these, 66 had dyskaryotic (40 mild, 16 moderate, 10 severe), 12 koilocytotic, and 24 negative cytological reports (15 with genital warts of the vulva, cervix or both, and nine with abnormal cervical appearance). The colposcope used was a Zeiss OPM1-1, with a range of

3 × to 15 × magnifications. The cervix was gently wiped with normal saline and examined through the colposcope to observe the topography, angioarchitecture, and surface contour; 3% acetic acid was then applied to accentuate the abnormal areas. Atypical transformation zones were identified by their characteristic appearances, such as mosaic, punctuation, acetowhite epithelium, leukoplakia, and other abnormalities of vasculature.[19] I noted if these changes were associated with non-condylomatous wart virus infection,[20] but made no attempt to grade CIN lesions. Biopsies were taken from atypical transformation zones, and histological features were reported as being either negative or consistent with HPV infection,[20] CIN alone, or CIN plus HPV infection.

## Results

Table I shows that 75 (3·7%) of the 2017 women screened had dyskaryotic smears. Of these, eight with mild and one with moderate dyskaryosis did not undergo colposcopy because they defaulted or clinic time was limited. The remaining 66 underwent colposcopy, as did an additional 12 women with koilocytotic smears and 24 with negative smears but with genital warts or abnormal cervical appearances.

TABLE I *Results of cytological screening and degree of dyskaryosis in 2017 women in five age groups*

| | | *No (%) with dyskaryosis:* | | | |
|---|---|---|---|---|---|
| *Age (years)* | *No Screened* | *Mild* | *Moderate* | *Severe* | *Total* |
| 15-19 | 395 | 13 | 2 | 2 | 17 (4·3) |
| 20-24 | 723 | 18 | 7 | 4 | 29 (4·0) |
| 25-29 | 407 | 6 | 6 | 1 | 13 (3·2) |
| 30-34 | 234 | 5 | 2 | 3 | 10 (4·3) |
| 35 and over | 258 | 6 | 0 | 0 | 6 (2·3) |
| Total | 2017 | 48 | 17 | 10 | 75 (3·7) |

Table II shows details of cytological, colposcopic, and histological findings in these women.

Biopsies were taken from 73 women who had atypical transformation zones. Of these, 34 had colposcopic features of non-condylomatous wart virus infection, which was confirmed histologically in 27 women, giving a 79·4% correlation. There were CIN lesions in 55 women (75%), in 30 (54·5%) of whom both CIN and non-condylomatous wart virus infection were reported on histological examination. Of 24 women with genital warts and CIN lesions, only 17 (70%) had histological evidence of associated non-condylomatous wart virus infection. Condylomatous lesions of the cervix were seen in one woman with CIN3 and in four with CIN2.

The degree of dyskaryosis on cytology was underestimated in 17 (16·6%) women who underwent colposcopy, and three with CIN lesions had negative cytology results. The false negative cytology rate was 2·9%. Additionally, 12 (30%) of 40 women with mild dyskaryotic cytology smears had CIN2 or CIN3 lesions on histology. Seven of the 11 patients with CIN3 lesions had had negative reports on cervical cytology smears performed in this clinic or elsewhere within the preceding two years. Of these, three were screened again at the discretion of the examining doctor.

Table III shows the ages of women with CIN lesions. All histologically confirmed CIN3 lesions were in women below the age of 35, giving an incidence of 0·63% in women under 35 and 0·55% of all women screened. The mean age of women with CIN1 was 23 (range 16-36) years, that for CIN2 was 25 (range 17-43), and for CIN3 was 27 (range 20-34). Women under 25 formed 78·2% of all women with CIN1, 76·1% of all those with CIN2, and 18·1% of all those with CIN3. Those under 20 formed 43% and 38% of women with CIN1 and CIN2 respectively.

TABLE II *Comparison of cytological, colposcopic, and histological findings in 102 women*

| *Results of cytological examination* | *Colposcopy undertaken in:* | *Biopsy results* | | *Results of histological examination* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *CIN only* | *CIN + NCWVI* | *Negative* | *Koilocytosis ("warty")* | *CIN1 only* | *CIN1 + NCWVI* | *CIN2 only* | *CIN2 + NCWVI* | *CIN3 only* | *CIN3 + NCWVI* |
| Dyskaryotic (n = 66) | | | | | | | | | | | |
| Mild | 40 | 15 | 19 | 2 | 4 | 3 | 13 | 3 | 7 | 2 | 0 |
| Moderate | 16 | 12 | 3 | 3 | 0 | 1 | 2 | 1 | 3 | 5 | 0 |
| Severe | 10 | 7 | 2 | 0 | 0 | 1 | 0 | 5 | 0 | 3 | 0 |
| Negative (n = 24) | | | | | | | | | | | |
| Abnormal | 9 | 2 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Warts | 15 | 2 | 5 | 1 | 4 | 1 | 1 | 0 | 0 | 0 | 0 |
| Koilocytosis | 12 | 1 | 4 | 1 | 1 | 0 | 1 | 0 | 2 | 0 | 0 |
| Total | 102 | 39 | 34 | 9 | 9 | 6 | 17 | 9 | 12 | 10 | 1 |

CIN = cervical intraepithelial neoplasia; NCWVI = non-condylomatous wart virus infection.

TABLE III *Results of histological examination in 2017 women in five age groups*

| Age (years) | No screened | Histological results | | | |
|---|---|---|---|---|---|
| | | CIN1 | CIN2 | CIN3 | Total |
| 15-19 | 395 | 8 | 4 | 0 | 12 |
| 20-24 | 723 | 10 | 12 | 2 | 24 |
| 25-29 | 407 | 2 | 2 | 6 | 10 |
| 30-34 | 234 | 2 | 1 | 3 | 6 |
| 35 and over | 258 | 1 | 2 | 0 | 3 |
| Total | 2017 | 23 | 21 | 11 | 55 |

Table IV shows the past and present STD profile of women with CIN lesions, of whom 24 (43·6%) had past or present genital warts. Of seven (12·7%) women with past or present genital herpes, five had either CIN2 or CIN3. Past or present multiple STD (three or more infections) were diagnosed in nine (16%) of the 55 women with CIN lesions.

## Discussion

The only report on the incidence of CIN and cancer of the cervix in an STD clinic was published in 1951, when an incidence of 2·08% was reported for CIN3 and carcinoma.[9] This group was characterised by a high incidence of syphilis (91%) and low socio-economic status. The lower incidence of 0·55% in women attending this clinic may be attributed to a changing clinic population. As taboos attached to the clinics are removed, more and more women of higher socioeconomic groups attend them, often seeking advice for conditions other than STD. Such women constitute 40% of our clinic population. The sexual freedom of the past 20 years and the earlier onset of sexual activity in women has increased the proportion of teenagers attending these clinics, altering the age distribution of women attenders. Nevertheless, it is possible that our selective screening procedure may have given a falsely low incidence rate.

TABLE IV *History of sexually transmitted diseases in relation to cervical intraepithelial neoplasia*

| Infection with: | Histological results | | | Total (% of total with CIN (n = 55)) |
|---|---|---|---|---|
| | CIN1 | CIN2 | CIN3 | |
| Human papillomavirus | 12 | 11 | 1 | 24 (43·6) |
| Herpes simplex virus | 2 | 3 | 2 | 7 (12·7) |
| *Neisseria gonorrhoeae* | 13 | 4 | 3 | 20 (36·3) |
| *Chlamydia trachomatis* | 5 | 5 | 4 | 14 (25·5) |
| *Trichomonas vaginalis* | 5 | 5 | 2 | 12 (21·8) |
| Multiple STD (three or more) | 3 | 4 | 2 | 9 (16·3) |

A disturbing feature is the underestimation of the pathological diagnosis by cytological examination alone, especially the false negative rate of 2·9%. Although it is possible that women attending STD clinics are also at risk of developing "rapid onset" carcinoma of the cervix, having recently had negative results of smears,[21] false negative rates of 1-30% have been reported.[22] We believe that women with any degree of dyskaryosis on cytological examination should undergo colposcopy, as biopsy tests of atypical transformation zones provide more accurate diagnoses.[23] Colposcopic investigation for the presence or absence of non-condylomatous wart virus infection may be inaccurate, a biopsy specimen should be taken routinely from any atypical transformation zone, as appropriate management is guided by the degree of CIN rather than the associated warty changes.

The overall incidence of CIN3 of 0·63% that we found in women under 35 is double the national average, which was 0·3% in 1980.[24] A reduction in the mean age of onset of CIN3 has been reported recently,[21 24] although our findings suggest that this may be even earlier in women attending STD clinics. Our finding of appreciable numbers of women aged under 20 with CIN1 and CIN2 indicates routine cervical cytology screening, irrespective of age in this group of women.

With the convincing epidemiological evidence linking previous HSV type II infection with cervical precancer,[10 14] it is surprising that only a small number of our patients with CIN had a history of genital herpes. Nevertheless, given the latent period between the acquisition of this infection and the development of CIN,[25] and the rising incidence of genital herpes,[26] we support the view that yearly cytology smears are necessary in infected women.

The association of HPV infection with 54·5% of CIN lesions in this study confirms the findings of Syrjanen,[27] although a recent study has found a 91% association.[28] There is no doubt that all women with genital warts need cytological screening. As the association of HPV infection with CIN is high, prolonged follow up of women with negative smear results may give valuable information.

Although the high proportion of affected women previously infected with *T vaginalis, Neisseria gonorrhoeae* and *C trachomatis* may relate to a common association with sexual activity and partner changing, women who have had recurrent multiple STD are at high risk of developing CIN and should preferably have yearly cytology smears.

I believe that colposcopy will be of value as an integral part of clinic practice in STD clinics, not only because women attending such clinics default and may be reluctant to attend other clinics, but also

because the majority of conditions associated with CIN of the cervix are seen at such clinics. It is, therefore, a very useful research tool.

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