

The Management of Minor Degrees of Cervical Dysplasia Associated with the Human Papilloma Virus

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This report attempts to define further the natural history of minor degrees of cervical dysplasia associated with human papilloma virus (HPV). Five hundred and twenty-five patients with a diagnosis of mild to moderate cervical dysplasia and HPV effects were followed *without treatment* for six months to five years. Those patients who progressed to a greater degree of dysplasia were removed from follow-up and treated appropriately. Those patients who regressed to a non-dysplastic state were returned to the original referring physician to be followed with annual cytology. Regression to a non-dysplastic state was 30.5 percent at six months, 50.4 percent at 1½ years, 60.5 percent at 2½ years, 70.9 percent at 3½ years, 77.3 percent at 4½ years, 7.8 percent have progressed to a greater degree of cervical dysplasia, removed from follow-up, and treated, and 22 patients have recurred, all with minor degrees of dysplasia. No invasive cancer has been diagnosed in this group of patients. From these results, we conclude that patients with minor degrees of dysplasia associated with HPV can be followed in a routine screening program with the anticipation that the great majority will, over time, convert to a non-dysplastic state. A small number of patients will progress to a higher degree of dysplasia and will be effectively identified, to be referred for colposcopic assessment and appropriate treatment.

Since Alex Meisels first associated the human papilloma virus (HPV) with cervical dysplasia [1], there has been an intense interest in the implications of such an association. This interest has become one of concern as a result of the observation by virologists that the "Human Papilloma Virus is necessary but not sufficient" [2] to the development of lower genital tract cancer. These concerns have resulted in the commonly accepted practice of referring all women with cytologically identified cervical dysplasia associated with human papilloma virus effects to colposcopy clinics for confirmation of diagnosis and treatment.

Approximately 3 percent of the female population of Canada who are ever coitally active will show some degree of cervical cytological atypia (HPV effects or more significant degrees of dysplasia) on cytological screening (Table 1). Less than 25 percent of those patients will show moderate dysplasia with or without human papilloma virus effects or more significant degrees of dysplasia. Before the enormous cost of colposcopic examination and treatment of this large group of patients with minor changes can be justified, a clear understanding of the natural history of this disease state and the ultimate risk of developing greater degrees of dysplasia and invasive disease is required.

The colposcopy clinic at the Kingston General Hospital (like other colposcopy

TABLE 1
 Combined One Year's Experience (1989) of Three Canadian Cytological
 Laboratories^a

	<i>n</i>	%
Total Smears	134,245	
Total Abnormal Smears, including HPV effects	3,967	3
Significant Abnormalities, moderate dysplasia with or without HPV effects or more significant degrees of dysplasia	930	.7

^aDouglas Laboratory, Ottawa, Ontario
 MDS Laboratory, Toronto, Ontario
 Hotel Dieu Hospital Laboratory, Kingston, Ontario

clinics in the early 1980s) noticed a significant change in its referral pattern. The number of patients with significant dysplasia decreased, to be overcompensated by a large group of patients (usually young) with minor degrees of cervical dysplasia associated with the human papilloma virus effects. The colposcopic picture was almost always benign and showed, to this author, little or no evidence to suggest that these women were at risk of developing greater degrees of dysplasia or invasive disease.

METHODS

Because of this skepticism regarding the implication of minor degrees of dysplasia associated with the human papilloma virus and the paucity of information regarding the natural history of this state, the colposcopy clinic at the Kingston General Hospital adopted the following practice policy:

1. All patients with mild to moderate dysplasia associated with the human papilloma virus identified by cytology or biopsy at the first clinic visit would be followed, without treatment, and reviewed at six-monthly intervals.
2. a. Patients whose degree of dysplasia progressed to severe dysplasia (with or without persistent human papilloma virus effects) or greater, identified either by cytology or biopsy, would be removed from follow-up and their lesions treated appropriately.
- b. Patients whose dysplasia disappeared (with or without persistent human papilloma virus effects), identified by cytology or biopsy, would be discharged to the referring physician with the request that annual cytology be obtained and the patient be returned to the colposcopy clinic should the dysplasia recur.
- c. Patients demonstrating mild to moderate dysplasia (with or without persistent human papilloma virus effects), identified by biopsy or cytology, would be considered unchanged and seen again in six months.

All patients referred to the colposcopy clinic at the Kingston General Hospital have demonstrated abnormal cervical cytology on a previous routine screening examination. All patients, at their first visit, had a colposcopic visualization of the cervix, repeat cytology, and biopsy of any abnormal areas. Patients were enrolled in this series if they demonstrated the human papilloma virus effects plus mild or moderate dysplasia either on biopsy or cytology. At each subsequent visit, the cervix

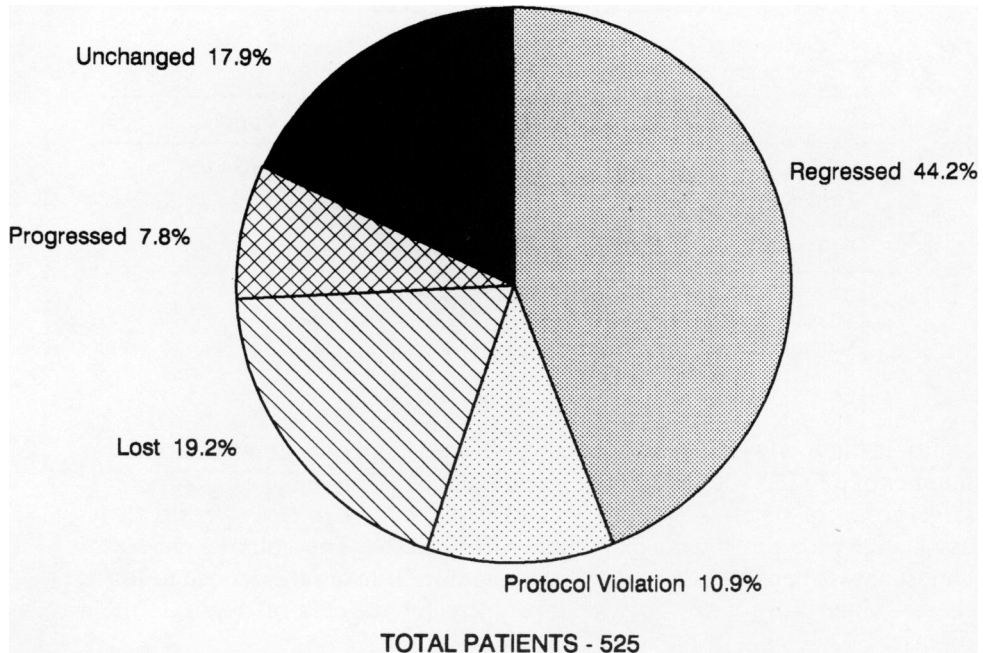


FIG. 1. Status of all patients six months after closure of the study. All patients were followed for six to 58 months, with a median follow-up of 30 months.

was colposcopically visualized and cytology repeated. Biopsies were taken if there was concern regarding possible progression of the dysplasia.

All cytological smears obtained at the colposcopy clinic, Kingston General Hospital, were screened by the Cytological Division of the Department of Pathology, Kingston General Hospital—Queen's University. All biopsies taken at the colposcopy clinic were read by the Division of Gynaecologic Oncology, Department of Pathology, Kingston General Hospital—Queen's University.

Human papilloma virus typing was not done. The lack of specificity in determining the outcome of minor degrees of dysplasia associated with the human papilloma virus infection does not justify the use of such testing on a routine basis [3,4].

This management policy was initiated September 1, 1985, and, for the purpose of this report, closed December 31, 1989.

RESULTS

Five hundred and twenty-five consecutive patients were enrolled in this series. All patients were followed for six to 58 months, with a median follow-up of 30 months. Figure 1 shows the status of all patients six months after closure of this series (June 30, 1990). Violations include inappropriate entry into the series, treatment elsewhere, and patient request for treatment. Lost are those patients who failed to keep their last appointments prior to June 30, 1990; many were seen subsequently.

Figure 2 shows the age distribution of this group. Fifty percent were under 25 years of age at the time of enrollment.

Figure 3 shows the spontaneous regression rate to a non-dysplastic state (with or without persistent HPV effects) at six-month intervals. The numbers at the top of the bars indicate the total number of patients followed to that particular interval, and the

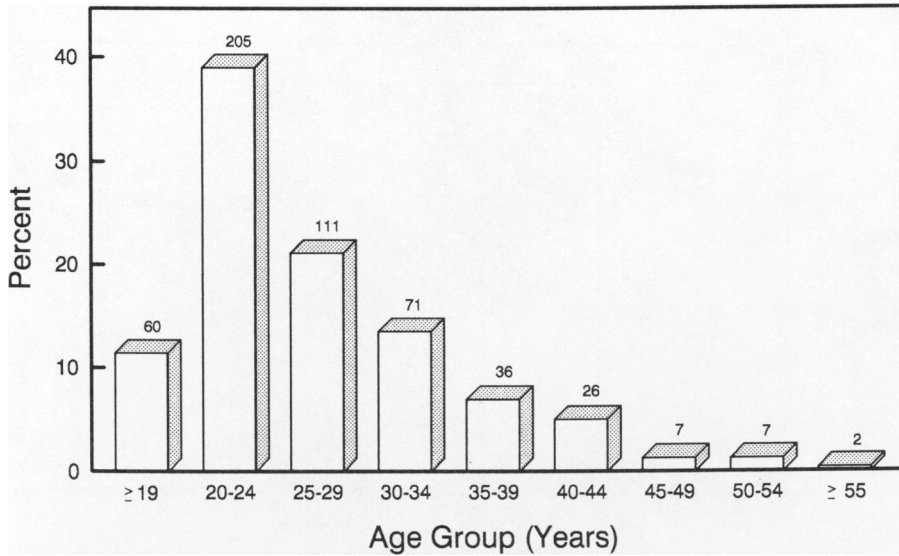


FIG. 2. Age distribution. Numerals at the top of the bar show the total number of patients in that age group.

solid portion of the bar indicates the percentage of those patients whose dysplasia disappeared with or without persistent HPV effects.

Figure 4 shows the number and time of recurrences. The frequency of recurrence appears to decrease with time and at 2½ years the abnormal cytology rate in this

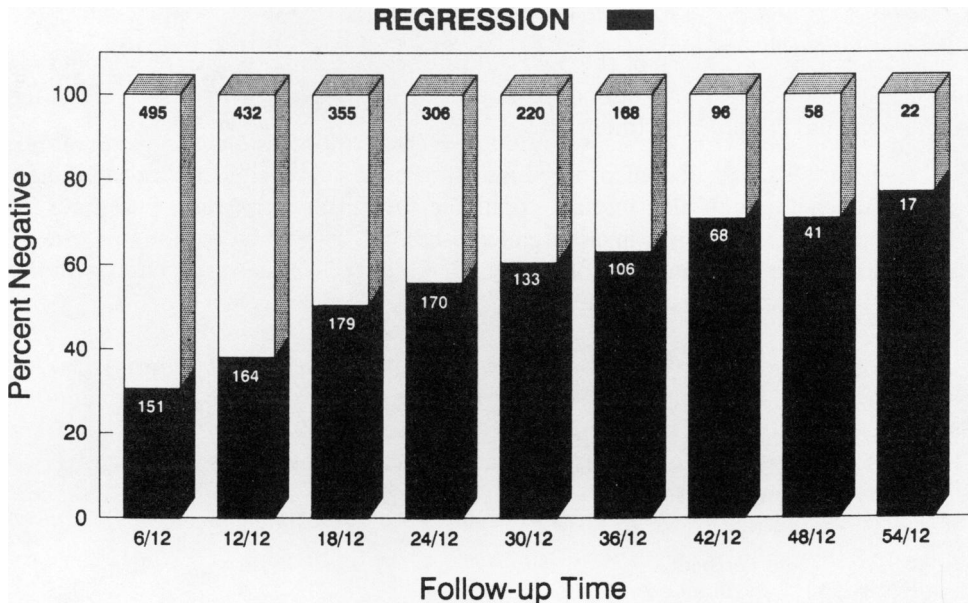


FIG. 3. Spontaneous regression to a non-dysplastic state (with or without persistent HPV). Numerals at the top of the bar denote the number of patients followed to that time period. The solid portion of the bar denotes the percentage that have reverted to a non-dysplastic state.

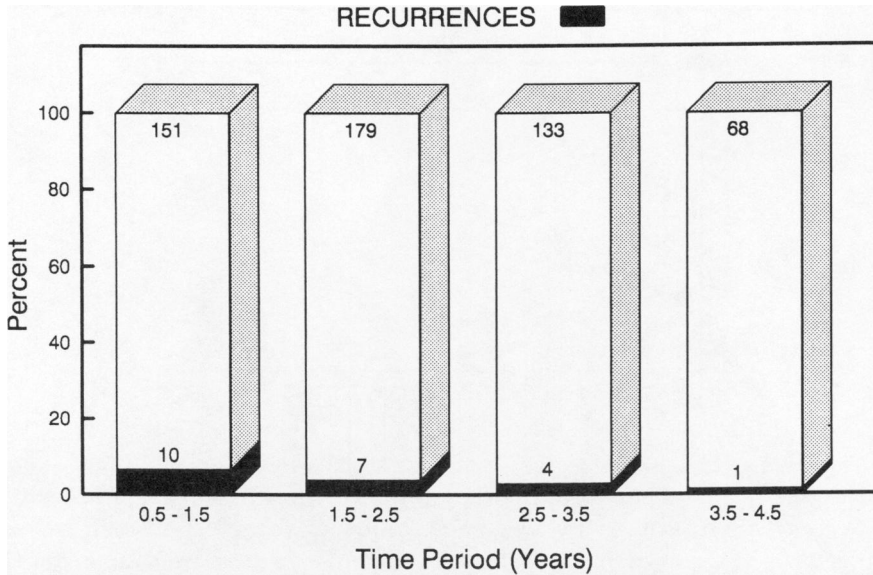


FIG. 4. Recurrences. Numerals at the top of the bars indicate the number of patients cytologically negative (with or without HPV effects) at the beginning of that time interval. The solid portion indicates the percentage recurring during that period.

population group is about the same as that of the population at large. All recurrences were of minor degrees, and none required treatment.

Table 2 shows the number of patients and time of progression to greater degrees of dysplasia. All patients who progressed were removed from follow-up and effectively treated. No patient progressed to invasive cancer.

DISCUSSION

The clinical justifications for the policy of referring all patients with minor degrees of dysplasia associated with human papilloma virus effects to colposcopy clinic for assessment and possible treatment are:

1. There is a high risk of progression from mild degrees of cervical dysplasia, associated with the human papilloma virus, to more severe degrees of dysplasia and even to invasive cancer [4,5].
2. There is a high rate of cytological undercall of dysplasias associated with the human papilloma virus effects [6].

TABLE 2
Progressions

Year	No.
First	25
Second	12
Third	4
Fourth	0
Total	41

TABLE 3
Distribution of Abnormal Smears^a

Status	No.
HPV only	95
Mild and HPV	206
Mild	650
Moderate and HPV	47
Moderate	170
Severe and HPV	2
Severe	69
Carcinoma in situ and invasive	25
Total smears	43,600

^aMDS Laboratories, Toronto, Ontario, 1989

Our experience does not support either of these concepts. As this series matured year by year, there was an overwhelming tendency for these women to revert spontaneously to a non-dysplastic state, dispelling the concern over the high risk of progression to greater degrees of dysplasia and invasive cancer. By the 4½-year anniversary date, three-fourths of these patients showed no evidence of dysplastic change.

The human papilloma virus may be necessary for the development of cancer of the cervix, but it is certain that this process is not the common pathway for the greater majority of women so affected [7]. Clearly some other, less common factor(s) or co-factor(s) is (are) required for these patients to progress to a greater degree of dysplasia or invasive cancer.

There were 41 patients who progressed to a more severe degree of dysplasia. Although the number of patients followed decreased with time, the suggestion here is that progression tends to be early rather than late. There is, of course, the possibility that some of these early progressions were initially undercalled at the time of their entering the series. Regardless of that possibility, the important fact is that those patients who did show a greater degree of dysplasia were identified in this dysplastic state before invasive disease developed.

The second concern—cytological undercall—in the presence of human papilloma virus effects, if indeed a fact, has little apparent practical implication, as evidenced by our experience with this series.

That the human papilloma virus does not mask significant dysplasia is suggested by the observation of Dr. Meisels [8] that cells showing significant dysplastic change (while still harboring the virus) tend not to show the cytologic effects of the virus. This latter observation would appear to be confirmed by the experience of a moderately sized Canadian cytological laboratory, which in 1989 read 43,600 smears; 96 of these showed a significant degree of dysplasia (severe or greater) and only two of these had concomitant HPV effects (Table 3)

The high incidence of genital HPV infection in contemporary society [9,10], the frequency with which this infection is associated with minor degrees of cervical dysplasia, and the benign colposcopic picture presented by these patients obliges one to ask if these minor dysplastic changes associated with the human papilloma virus seen on cytologic examination are truly dysplastic change or simply “viral effects”

that disappear when the viral infection itself disappears or, if true dysplasia, that disappear when the infection disappears?

The fact that over 50 percent of our patients were under 25 years of age at the time of their initial colposcopic assessment is in keeping with the experience of others [11] and confirms the clinical impression that the human papilloma virus infection (with or without identifiable dysplastic change) is characteristically seen in the young, recently coitally active population, which, in turn, suggests that the human papilloma virus, like other virus infections, spontaneously regresses (along with the minor dysplastic picture) over time, as the individual develops her own defense mechanism.

CONCLUSIONS

Based on these observations and our experience with conservative management, minor degrees of dysplasia, over a period of 4½ years, we suggest that:

1. Patients with minor degrees of cervical dysplasia associated with human papilloma virus effects can be confidently followed in a routine screening program, with the expectation that the overwhelming majority will eventually revert to a non-dysplastic state, and
2. Those women who do progress to a greater degree of dysplasia will effectively be identified in a screening program, to be referred for colposcopic assessment and appropriate treatment.

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