Natural History of Established Low Grade Cervical Intraepithelial (CIN 1) Lesions

NISHA BANSAL, JASON D. WRIGHT, CARMEL J. COHEN and THOMAS J. HERZOG

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology,
Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.

Abstract. *The aim of the present study was to ascertain the natural history of cervical intraepithelial lesions 1 (CIN 1) and to develop recommendations to optimize follow-up. Patients and Methods: Patients referred for colposcopy from January, 1996 to July, 2005 were reviewed. A prospectively maintained database was quarried for demographic, clinical, and pathologic data. Results: The cohort included 1,001 patients with CIN 1. At 6 months, 330 patients (49%) regressed to normal, 305 (45%) had persistent low grade, while 45 (7%) progressed to high grade lesions. At 12 months, of those with negative pathology at 6 months, 200 (80%) remained negative, 42 (16%) demonstrated low grade and 9 (4%) progressed to high grade lesions. Of those with low grade lesions at 6 months, 131 (50%) regressed, 121 (46%) had persistent low grade, and 10 (4%) progressed to high grade lesions. Conclusion: Our data demonstrates a low rate of progression for CIN 1, suggesting it may be reasonable to prolong the screening interval in women with CIN 1.*

The estimated annual incidence of cervical cancer in the United States in 2007 is 11,150 cases, with approximately 3,670 deaths from the disease (1). In developing countries cervical cancer represents the second most common cause of cancer related morbidity and mortality with 409,000 cases annually (2). The dramatic decline in the incidence and mortality from cervical cancer in Western countries can be attributed to the institution of effective cervical cancer screening programs. The successful implementation of these screening programs is based on the assumption that cervical intraepithelial lesions (CIN) progresses through a long

preinvasive state prior to the development of invasive cancer. Screening programs allow for the detection of these preinvasive lesions which can easily be effectively treated.

Cervical cytologic screening, while instrumental in the reduction of cervical cancer incidence and mortality, is also fraught with potential errors. Screening can lead to unnecessary visits, procedures and generate patient anxiety. Furthermore, unnecessary screening tests contribute to increased cost without offsetting patient benefit. It is therefore important to determine the optimal interval of screening and follow-up of abnormal preinvasive lesions. Understanding the natural history of these abnormalities can help elucidate the optimal management of abnormal screening tests. We hypothesize that due to the high rate of spontaneous regression of low grade cervical intraepithelial lesions that current follow-up programs could be simplified. The purpose of this study is to ascertain the natural history of CIN 1 lesions and to develop recommendations for follow-up for women with CIN 1.

Patients and Methods

After institutional review board approval was obtained, all patients who were referred to the Colposcopy Clinic at the Columbia Presbyterian Medical Center from January 17, 1996 to July 22, 2005 were screened for study eligibility. Patient demographic information including age, referral cytology results and pathologic data were collected prospectively and maintained in an electronic database. All cytology and pathology specimens were read at our institution. Patients with histologically confirmed CIN 1 lesions at initial colposcopy were eligible for study inclusion.

The clinic follow-up protocol during this time period called for repeat cytology with colposcopy every six months for all patients with previously diagnosed abnormalities. Patients returned to annual screening after 2 screening tests 6 months apart were normal. Patients who did not return for follow up examinations were contacted by phone or mail to reschedule their appointment. A total of three attempts to contact each patient were made, with the third attempt being by certified letter. Chronologic follow-up data was compiled and analyzed for regression, persistence or progression of lesions over time. Regression was defined as CIN 1 lesions reverting to normal cytology and either negative biopsy or normal colposcopy without biopsy. Disease persistence was

Correspondence to: Nisha Bansal, MD, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, 161 Fort Washington Ave, 8th Floor, New York, NY 10032, U.S.A. Tel: +212 305 3410, Fax: +212 305 3412, e-mail: nishabansal1@yahoo.com
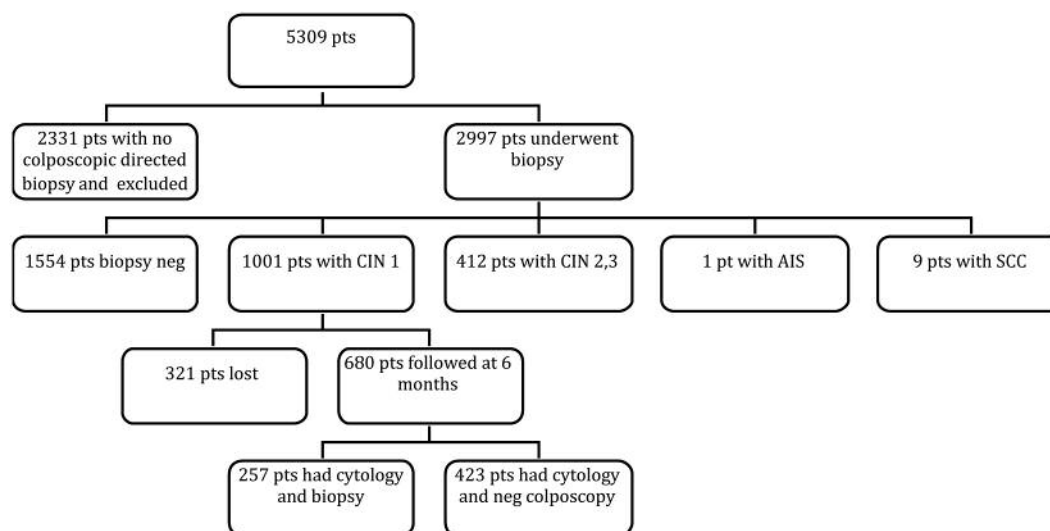
Figure 1. *Algorithm of study population.*

defined as CIN 1 lesions that were again demonstrated on biopsy, or ASC-US or LSIL cytology. Progression was defined as biopsy confirmed CIN 2, 3, AIS, cancer or HSIL or ASC-H cytology. Statistical analysis was performed using the Student's *t*-test and Chi-square test.

Results

A total of 5,309 patients were referred for colposcopy during the indicated time period. The mean age of the population was 29.3 years. Of referred subjects, 2,331 patients who underwent colposcopy did not have a biopsy performed. Of the 2,977 patients who underwent colposcopically directed biopsy 1,554 had negative pathology, 1,001 had CIN 1, 412 had CIN 2 or 3, 1 had adenocarcinoma in situ (AIS), and 9 had squamous cell carcinoma (SCC) (Figure 1). The 1,001 subjects with CIN 1 comprise the study cohort. The mean age of those with biopsy confirmed lesions was 27.1 years. Patients with biopsy confirmed lesions were significantly younger than the entire population referred for colposcopy (p=0.0001).

Of the 1,001 patients with biopsy confirmed CIN 1, 321 patients (32%) were lost to follow up. Follow up was available for 680 (68%) of the patients with CIN 1. Of these women, 257 patients (38%) had cytology and a colposcopically directed biopsy at 6 months, while 423 patients (62%) were evaluated by cytology and colposcopy without biopsy. The decision to perform or defer biopsy was made at the discretion of the attending colposcopist, and was based on colposcopic exam. A total of 330 patients (49%) with histologically confirmed CIN 1 were found to regress to negative at 6 months (Table I). A total of 305 patients (45%) had persistent disease 6 months; 95 patients by

biopsy, and 130 patients by cytology with negative colposcopy. A total of 45 patients (7%) with CIN 1 progressed to high grade lesions at the 6 months; 40 patients by biopsy and 5 patients by cytology with negative colposcopy. CIN 1 patients who underwent biopsy at the 6 month follow-up were significantly older than those who did not (27.9 *vs.* 26.0, p=0.0012).

Of the 635 patients with negative lesions or persistent low grade lesions at the 6 month visit, a total of 513 patients (81%) returned for follow-up examination at one year. Of these patients, a total of 191 patients underwent cytology with colposcopically directed biopsy while 322 patients were evaluated by cytology with colposcopy without biopsy. The follow-up rate at one year was significantly higher than the follow-up rate at 6 months (68% *vs.* 81%, p=0.001). This indicates that once patients were established in the clinic, with at least two prior visits, they were more likely to return for follow up exam.

Of the 513 patients who returned for their 12 month follow-up examination, 251 had negative pathology at their 6 month visit. Among these 251 patients, 200 (80%) remained negative, 42 (16%) demonstrated low grade lesions and 9 patients (4%) progressed to high grade lesions (Table II). The remaining 262 patients who returned for 12 month follow-up had low grade lesions at the 6 month time point. Of these 262 subjects, 131 patients (50%) regressed to negative, 121 patients (46%) had persistent low grade lesions, and 10 patients (4%) progressed to high grade lesions. Women with persistent low grade lesions at 6 months were more likely to have a low grade abnormality detected at 12 months than those patients with negative pathology at 6 months (46% *vs.* 16%) (p<0.0001). Of note, 19 patients (3.7%) were found to have high grade lesions at one year.

Table I. *Six month follow-up results.*

	Total (n=680)	Cytology (n=423)	Histology (n=257)
Negative	330 (48.5)	208 (49.2)	122 (47.5)
Low grade	305 (44.9)	210 (49.6)	95 (37.0)
High grade	45 (6.6)	5 (1.1)	40 (15.6)

Table II. *Twelve month follow-up results.*

Test result	6-month pathology negative (n=251)	6-month pathology low grade (n=262)	p
Negative	200 (79.7)	131 (50.0)	<0.0001
Low grade	42 (16.7)	121 (46.2)	<0.0001
High grade	9 (3.6)	10 (3.8)	0.89

This is compared to 45 (6.6%) who progressed to a high grade lesion at 6 months. Ultimately a total of 10.3% of patients with CIN 1 had evidence of high grade lesions within one year. No cases of invasive cancer were identified at either 6 months or at one year.

Discussion

An understanding of the natural history of low grade cervical intraepithelial lesions is central to optimizing screening and triage of patients, and to the management of cervical dysplasia. Aside from the degree of dysplasia, many other factors influence the course of cervical intraepithelial neoplasia including environmental factors, tobacco use, immunologic factors and the presence of high risk HPV types.

Results of previous studies have indicated that a large number of low grade cervical intraepithelial lesions will spontaneously regress (3-6). A meta-analysis representing 27,929 patients, found that the rate of regression to normal was 68% for women with ASCUS, 48% for LSIL and 35% for HSIL (7). The rate of progression to HSIL at 24 months was 7% for ASCUS and 21% LSIL (7). The rate of invasive cervical cancer at 24 months was 0.25% for ASCUS, 0.15% for LSIL and 1.44% for HSIL (7). These findings suggest that the risk of progression to invasive cancer over 24 months is small for women with low grade cervical abnormalities. A comprehensive literature review of patients with CIN 1 found that spontaneous regression occurred in 57% of patients while progression was noted in 11% (6). A cohort study of more than 17,000 women with CIN found that spontaneous regression of CIN 1 in 44% of patients within 2 years and in 74% after 5 years of follow-up (4). These studies suggest that the majority of low grade cervical lesions will regress within 2 years and support observation. Our study confirms these findings in a large group of patients with histologically confirmed CIN 1. Overall, 52% of CIN 1 patients regressed within 1 year while 10% progressed to high grade disease.

Despite the large number of patients included in our analysis, this study suffers from the usual limitations of retrospective studies. A substantial number of patients failed to return for follow-up. While loss to follow-up is common in cervical dysplasia studies, our colposcopy clinic made every effort to optimize return follow-up. Unlike the majority of studies of CIN 1 our study has the strength that all patients underwent repeat colposcopy in addition to cytologic sampling. However, biopsy was only performed in patients with visible lesions. Given that all patients were not biopsied we cannot exclude the possibility that a small number of high grade lesions were potentially not identified. Finally, we were unable to account for the presence of other factors which influence the natural history of cervical dysplasia such as HPV type, cigarette smoking and sexual risk factors (11-15).

Current ASCCP recommendations for the follow-up of women with CIN 1 call for repeat cytology at 6 and 12 months or HPV testing at 12 months (8-10). After two negative cytologic samples or a negative HPV test, the recommendation is to return to annual screening (8-10). Overall, we found a low rate of progression to high grade disease among our subjects with CIN 1. After 12 months of follow-up, 10.3% of the patients had documented high grade lesions. Of those who progressed, 6.6% of the high grade lesions were noted at 6 months while the remaining 3.7% were identified at the 12 month examination. No cases of invasive cancer were seen. Based on the low rate of progression of CIN 1 it would appear reasonable to omit 6 month follow-up in women with CIN 1. Those patients with biopsied confirmed CIN 1 and an adequate colposcopy could return to annual screening with HPV testing at 12 months. Lengthening the screening interval in this group of patients avoids unnecessary visits and pathology samples as well as alleviates patient anxiety. Based on our findings such a strategy would have a minimal overall effect on the detection of high grade lesions. Additionally, the chance of progression of CIN 2 or 3 to cancer if follow-up is delayed by 6 months appears to be exceedingly low (8, 12).

In summary, our data reaffirms that there is a low rate of progression of low grade cervical lesions. While a number of factors influence the natural history of low grade cervical lesions, our data suggests that it may be reasonable to prolong the screening interval in women with CIN 1. Further prospective study to examine the pathologic outcomes, quality of life and costs associated with alternate follow-up schemas is warranted.

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