Original Article

# Expectant Management Versus Immediate Treatment for Low-Grade Cervical Intraepithelial Neoplasia

## A Randomized Trial in Canada and Brazil

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**BACKGROUND:** The optimal management strategy for women with low-grade biopsy-proven cervical intraepithelial neoplasia (CIN) is not clear. Our objective was to compare the effectiveness of regular colposcopic follow-up and treatment of progressive disease only versus immediate treatment. **METHODS:** Data were accrued between November 2000 and March 2006 for a noninferiority randomized clinical trial of 415 women with biopsy-proven grade 1 CIN from 8 Canadian and 2 Brazilian colposcopy clinics. Subjects were randomly assigned to either undergo immediate treatment with a loop electrical excision procedure (LEEP) or receive regular colposcopic follow-up for 18 months. The primary outcome was progression of disease to CIN 2 to 3 was based on histology obtained during 18 months of follow-up. Treatments were compared using differences of proportion with a 9% noninferiority margin. Analysis was conducted on the basis of intention-to-treat. **RESULTS:** An initial LEEP was performed on 179 women. Disease progression was found in 32. Easily controlled vaginal bleeding occurred in 16 (8.9%). During follow-up, disease progression was identified in 3 (1.7%) women in the immediate treatment arm and 9 (4.4%) in the colposcopic follow-up arm—a tolerable difference of 2.7% with 1-sided 95% confidence interval (CI) upper limit of 6.0%. Compliance with all 3 follow-up visits was 61% overall, but significantly worse in women $\leq$30 years of age ($P < .05$). **CONCLUSIONS:** The risk of progression to CIN grade 2 or 3 or cancer over 18 months was similar in the 2 treatment groups. In Canada and Brazil, follow-up for 18 months is a reasonable management strategy for women with persistent low-grade cytology who are found to have grade 1 CIN on referral for colposcopy and cervical biopsy. ***Cancer*** **2011;117:1438–45.** © *2010 American Cancer Society.*

**KEYWORDS:** Low grade intraepithelial neoplasia of the cervix, CIN 1.

**The** optimal management of women with low-grade biopsy-proven cervical intraepithelial neoplasia (CIN) is not clear. A 1998 Canadian survey reported that 46% of gynecologists who performed colposcopy would immediately treat women with grade 1 CIN (CIN1), whereas 42% would follow-up with colposcopy every 6 months and intervene only at

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progression of the epithelial dysplasia.[1] A systematic review (mostly case series) of women who presented with CIN1 on cytology showed that, within 24 months, 21% of cases progressed to CIN2 or 3, 0.15% progressed to invasive cancer, 47% regressed to normal, and the remainder persisted at the same level.[2,3,4]

For women with biopsy-proven CIN1, the advantage of a follow-up strategy using repeated colposcopy is that only those with persistent CIN1 or high-grade disease are treated. The disadvantage is that the protracted surveillance increases patient inconvenience, anxiety, and noncompliance.[5] The benefit of an immediate treatment (IT) strategy is that CIN1 and any other undetected CIN lesions are treated. The disadvantage of IT is that many women are over-treated and have a risk of bleeding, pelvic infection, altered fertility, cervical stenosis, or adverse obstetrical outcomes.[6,7]

Thus, we undertook a randomized trial of women with CIN1, comparing a strategy of regular colposcopic follow-up (CFup) with IT via loop electrosurgical excisional procedure (LEEP).

## MATERIALS AND METHODS

Women with biopsy-confirmed CIN1 were randomly assigned to undergo either CFup at 6, 12, and 18 months or IT with LEEP and follow-up for 18 months. If there was progression of CIN during follow-up, patients underwent LEEP. Subjects were recruited from 8 colposcopy clinics across Canada and 2 clinics in Brazil. Written informed consent was obtained from all enrolled patients. The study protocol was approved by the institutional review board at each participating center.

### *Patients*

Women who were referred to a colposcopy clinic for low-grade cytology smears underwent colposcopy with acetic acid. The worst cervical lesion was biopsied. Patients were eligible for the trial if they had CIN1 confirmed histologically by a study-approved center pathologist[8]; CIN1 was the highest grade lesion present; the lesion was confined to the cervix and completely observed; and patients were aged 16 years (14 years in Brazil) or older. Patients were excluded for any of the following: index PAP smear showed CIN2, CIN3, or cancer (CIN2/3/cancer), atypical glandular cells of unknown significance, or glandular dysplasia requiring immediate investigation; extension of the CIN1 lesion to the vagina, a separate vaginal lesion showing dysplasia, or a colposcopically-visible condyloma outside of the transformation zone; known allergy to local analgesics; unsatisfactory colposcopy (defined by inability to see the extent of the lesion in the endocervical canal or absence of a lesion on the ectocervix, but endocervical curettage shows CIN1); currently pregnant; prior therapy for dysplasia including medical (5FU), surgical (laser, LEEP), or cryotherapy; prior gynecologic cancer, pelvic radiation; other malignancies except nonmelanoma skin cancer; immunosuppressed because of diseases such as AIDS, organ transplantation, or on immunosuppressive medications (such as prednisone, imuran, or chemotherapy); already in a surveillance program for biopsy-proven CIN1; unable to attend follow-up visits because of geographic inaccessibility; cognitively impaired or otherwise unable to provide written informed consent.

### *Randomization and Intervention*

Randomization was performed centrally by contacting the Ontario Clinical Oncology Group coordinating center located in Hamilton, Canada. Women were stratified according to age ($\leq$30, $>$30 years) and center. Subjects were allocated to either arm in a 1:1 ratio using a computer-generated permuted-block randomization schedule.

Women randomized to IT received a superficial LEEP within 12 weeks after randomization. By using local anesthetic, LEEP was conducted after the application of 3%-5% acetic acid, with or without Lugol's solution, according to local policy.

### *Follow-Up and Outcomes*

At the follow-up visits, scheduled at 6, 12, and 18 months from the date of randomization, patients in both arms underwent cervical cytology, HPV testing of cervix and vagina using the Hybrid Capture 2 High-Risk HPV DNA Test (Digene Corporation, Gaithersburg, MD), and a colposcopy examination. Women were no longer followed if they were diagnosed with biopsy-proven CIN2/3/cancer. Procedures for contacting patients who failed to return for their scheduled visits were country-specific. In Canada, up to 5 attempts were made to contact the patient by phone over a 3-week period; a registered letter was sent to the home; and, finally, a letter was sent to the referring physician. In Brazil, a social worker was sent to meet with the patient to ensure the availability of adequate transportation and child care.

Before the trial commenced, colposcopists were asked to define the worst lesion on a set of 50 cervigrams.[9] In addition, pathologists classified 56 histology slides representing cervical biopsies stained with hematoxylin and

eosin as either benign, LSIL, HSIL, or other. To participate in the trial, the colposcopist and pathologist had to achieve good agreement (ie, a kappa statistic of at least 0.70), with the consensus classification of an expert panel of colposcopists or gynecologic oncology pathologists.[8]

The primary outcome was progression of disease from CIN1 to CIN2/3/cancer by histology during follow-up, and the secondary outcome was persistence of CIN1 after 18 months of follow-up by histology or cytology.

### *Statistical Analysis*

Sample size was established from case series that estimated the detection rate of CIN2/3/cancer by cytologic and/or histologic criteria of 12%, using colposcopic follow-up,[3] and 0% during follow-up after IT.[10] An information survey of colposcopists and policymakers formed a consensus opinion that a 9% difference in the presence of high-grade disease after 18 months between management strategies was the largest tolerable effect where IT would be preferable, and a 5% or less difference would decide in favor of the CFup approach. Assuming 1% of patients would have high-grade disease detected with IT, we desired 85% power to rule out a rate of 10%. This would be clinically unacceptable in the CFup arm (a noninferiority margin of 9%) with a smaller acceptable risk difference of 5% or less. With a 1-sided alpha of 5%, and allowing for 10% loss to follow-up, we needed 442 patients per arm to demonstrate the noninferiority of CFup relative to IT.[11,12]

The primary analysis, adhering to the intention-to-treat principle, counted CIN2/3/cancer outcomes during follow-up that were confirmed using histology (excluding women with disease progression detected on the initial LEEP). Secondary analyses included comparisons between groups of all disease progression postrandomization and CIN1 persistence (histologically or cytologically-confirmed CIN1 at 18 months). Because some patient drop-out was expected during follow-up, we performed a sensitivity analysis whereby outcomes were over-counted in the experimental CFup arm, assuming that the lost patients would contribute no additional events in the IT arm—thereby deliberately giving an advantage to the conventional IT approach.

For progression and persistence outcomes, 2-sided 90% confidence intervals, equivalent to a 1-sided 95% CI for the difference between proportions (CFup minus IT), were calculated using an exact binomial unconditional procedure (corresponding p-values were derived from an unconditional test based on the score statistic). Analysis was undertaken using StatXact 8.0 (Cytel Inc., Cambridge, MA) and SAS 9.1 (SAS Institute, Cary, NC).

## RESULTS

Between November 2000 and March 2006, 3934 patients were assessed for eligibility, 89% were excluded (Fig. 1), and 415 women from 8 Canadian and 2 Brazilian centers agreed to participate and were randomized: 209 to the IT arm and 206 to CFup arm. The trial was closed before achieving the target sample size of 884 patients because of the protracted time for recruitment. Baseline characteristics were similar between the two arms (Table 1). Canadian women, however, had higher levels of education, smoking, and income, and a lower number of children. They also had larger lesions and were more likely to be HPV positive.

At baseline, oncogenic HPV was identified on the cervix in 63% and in the vagina in 28% of the women enrolled. For the cervix, a single oncogenic HPV type was seen in 42%, 2 types in 27%, 3 types in 17%, and up to 10 types in 1 patient. The oncogenic types in order of frequency were HPV-16 (18%), HPV-53 (14%), HPV-52 (13%), HPV-51 (11%), HPV-56 (10%), HPV-18 (8%), and HPV-58 (8%). HPV-16 (26% vs 19%) and HPV-39 (15% vs 7%) were more prevalent in Canadian women, whereas HPV-53 (18% vs 10%) was more common in Brazilian women.

Of the 209 women randomized to IT, 177 (85%) received an initial LEEP, 23 (11%) did not have a LEEP, and 9 (4%) did not return after randomization. The histology of the LEEP was benign in 44 cases (25%), CIN 1 in 98 (55%), CIN 2/3 in 30 (17%), Cancer in 1 (1%), and other in 4 (2%). Of the 206 women randomized to CFup, 190 (92%) entered follow-up and 16 (8%) did not return after randomization. Two women deviated from the protocol and had initial LEEPs performed.

Patterns of follow-up in both groups are shown in Figure 1. Overall, 61% of study subjects were fully compliant by attending all 3 follow-up visits, 19% made 2 visits, 14% had 1 visit, and 6% had no follow-up visits. Compliance varied by strategy (55% IT vs 66% CFup), by country of origin (67% Canada vs 56% Brazil), and by age (75% for $>30$ vs 55% for $\leq 30$ years). Only age was a statistically significant factor. As expected, there were more missed follow-up visits in the IT arm: 24 (11%) never returned for any of their scheduled colposcopic follow-up visits, compared with none in the CFup group.

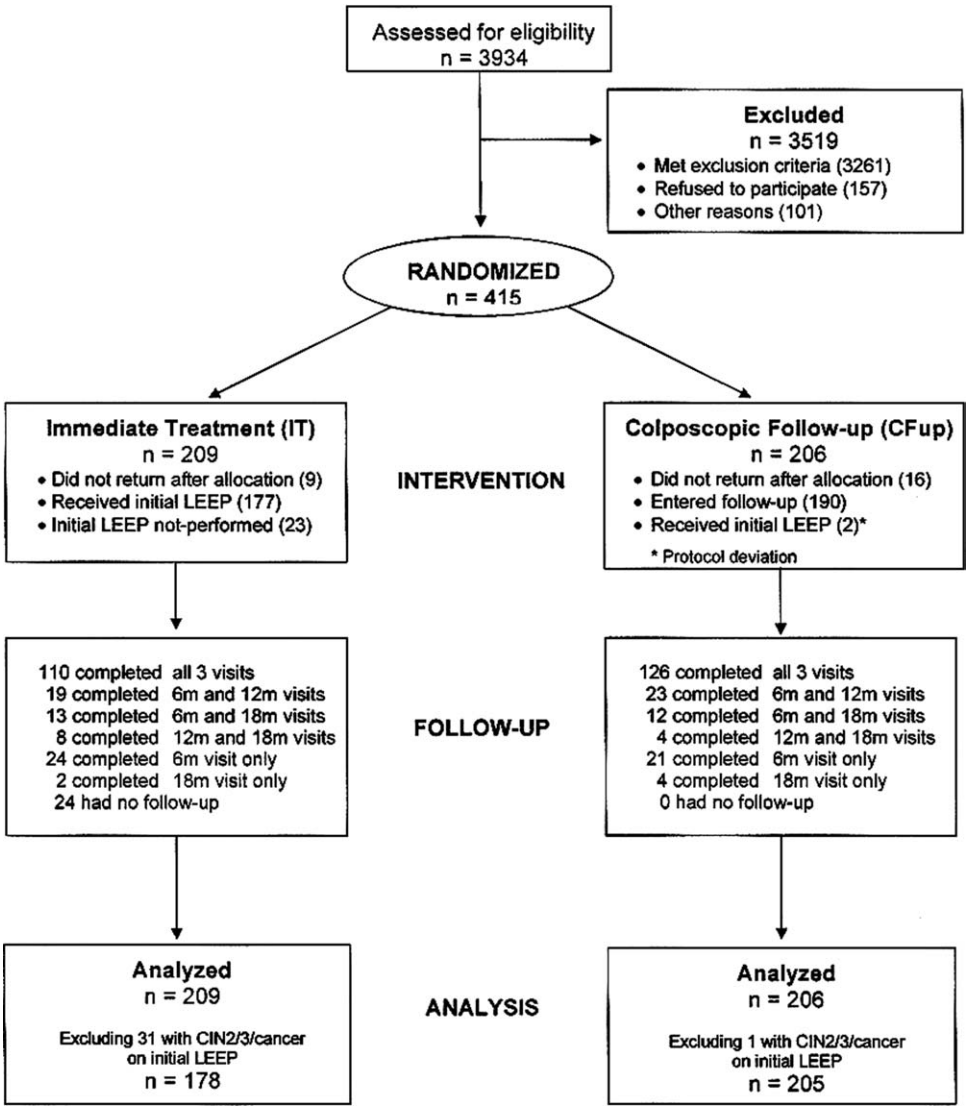


**Figure 1.** Study flow diagram.

Of the 177 IT women who had an initial LEEP, 31 (17.5%) showed disease progression (only 1 had cancer). Of the 169 women in the IT arm entering follow-up, only 3 (1.8%) developed CIN2/3 by 18 months; none of these 3 women had an initial LEEP.

Of the 206 women in the CFup group, 10 (4.9%) showed disease progression: 1 of the 2 subjects who had an initial LEEP, and 9 others who presented with CIN2/3 over the 18-month follow-up (3 at each follow-up visit).

Of the 179 women who underwent an initial LEEP, there were 16 (8.9%) cases of vaginal bleeding. However, no women had to return to the operating room.

### *Disease Progression*

During the 18-month follow-up period (including all randomized subjects except those showing CIN 2 or worse at the initial LEEP), 3 of the 178 women (1.7%) in the IT arm and 9 of the 205 (4.4%) in the CFup arm progressed to CIN2/3. The difference in these proportions (2.7%, 90% CI, −0.3% to 6.0%), which reflects the primary efficacy analysis, satisfies the criterion for the noninferiority of the CFup arm because the upper bound does not exceed 9% ($P = .0022$). If the initial LEEP outcomes are included, 34 of 209 women in the IT arm (16.3%) and 10 of 206 women in the CFup arm (4.9%) progressed to CIN2/3/cancer. This −11.4% difference (90% CI,

**Table 1.** Baseline Characteristics by Treatment and Country

| Characteristic | By Treatment | | By Country | |
|---|---|---|---|---|
| | CFup (*n=206*) | IT (*n=209*) | Canada (*n=167*) | Brazil (*n=248*) |
| **Age (years):** | | | | |
| *median (minimum-maximum)* | 26 (16-63) | 24 (14-65) | 26 (17-65) | 24 (14-59) |
| ≤30*: no. (%)* | 147 (71) | 153 (73) | 112 (67) | 188 (76) |
| >30*: no. (%)* | 59 (29) | 56 (27) | 55 (33) | 60 (24) |
| **Marital status: *no. (%)*** | | | | |
| Never married | 85 (41) | 93 (45) | 84 (50) | 94 (38) |
| Married/common law | 88 (43) | 86 (41) | 61 (37) | 113 (46) |
| Separated/divorced | 21 (10) | 18 (9) | 18 (10) | 21 (8) |
| Other | 12 ( 6) | 12 (6) | 4 (2) | 20 (8) |
| **N of children: *no. (%)*** | | | | |
| None | 93 (45) | 101 (48) | 103 (62) | 91 (37) |
| 1 to 3 | 94 (46) | 92 (44) | 54 (32) | 132 (53) |
| 4 or more | 16 (8) | 13 (6) | 8 (5) | 21 (8) |
| Unknown | 3 (1) | 3 (1) | 2 (1) | 4 (2) |
| **Education[a]: *no. (%)*** | | | | |
| Public school | 52 (25) | 46 (22) | 0 (0) | 98 (40) |
| Some high school | 37 (18) | 36 (17) | 13 (8) | 60 (24) |
| Completed high school | 31 (15) | 43 (21) | 34 (20) | 40 (16) |
| Some college | 16 (8) | 16 (8) | 20 (12) | 12 (5) |
| Completed college | 26 (13) | 32 (15) | 37 (22) | 21 (8) |
| Some university | 12 (6) | 17 (8) | 25 (15) | 4 (2) |
| Completed university | 26 (13) | 14 (7) | 35 (21) | 5 (2) |
| Unknown | 6 (3) | 5 (2) | 3 (2) | 8 (3) |
| **Smoking: *no. (%)*** | | | | |
| Yes | 54 (26) | 59 (28) | 56 (34) | 57 (23) |
| No, quit | 40 (19) | 29 (14) | 40 (24) | 29 (12) |
| No, never smoked | 110 (53) | 116 (56) | 68 (41) | 158 (64) |
| Unknown | 2 (1) | 5 (2) | 3 (2) | 4 (2) |
| **Household income[b]: *no. (%)*** | | | | |
| <20,000 | 142 (69) | 148 (71) | 62 (37) | 228 (92) |
| 20-40,000 | 29 (14) | 28 (13) | 44 (26) | 13 (5) |
| 40-60,000 | 11 (5) | 13 (6) | 22 (13) | 2 (1) |
| 60-80,000 | 11 (5) | 11 (5) | 20 (12) | 2 (1) |
| >80,000 | 8 (3) | 4 (1) | 12 (7) | 0 (0) |
| Unknown | 5 (2) | 5 (2) | 7 (4) | 3 (1) |
| **Index pap smear: *no. (%)*** | | | | |
| Benign | 16 (8) | 27 (13) | 18 (11) | 25 (10) |
| Low grade | 162 (79) | 152 (73) | 115 (69) | 199 (80) |
| High grade or cancer | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Other | 25 (12) | 24 (11) | 32 (19) | 17 (7) |
| Unknown | 3 (1) | 6 (3) | 2 (1) | 7 (3) |
| **Size of Lesion: *no. (%)*** | | | | |
| 1 quadrant | 109 (53) | 116 (56) | 70 (42) | 155 (63) |
| 2 quadrant | 58 (28) | 68 (33) | 62 (37) | 64 (26) |
| 3 quadrant | 10 (5) | 6 (3) | 7 (4) | 9 (4) |
| 4 quadrant | 25(12) | 15 (7) | 26 (16) | 14 (6) |
| Unknown | 4 (2) | 4 (2) | 2 (1) | 6 (2) |
| **Biopsy removed lesion: *no. (%)*** | | | | |
| Yes | 38 (18) | 48 (23) | 3 (2) | 83 (33) |
| No | 147 (71) | 150 (72) | 149 (89) | 148 (60) |
| Unknown | 21 (10) | 11 (5) | 15 (9) | 17 (7) |

(Continued)

Table 1. (Continued)

| Characteristic | By Treatment | | By Country | |
|---|---|---|---|---|
| | CFup (*n=206*) | IT (*n=209*) | Canada (*n=167*) | Brazil (*n=248*) |
| **ECC performed: *no. (%)*** | | | | |
| Yes | 1 (0) | 6 (3) | 7 (4) | 0 (0) |
| No | 204 (100) | 203 (97) | 160 (96) | 247 (100) |
| **Prior pap smears: *no. (%)*** | | | | |
| Incident[c] | 6 (3) | 5 (2) | 7 (4) | 4 (2) |
| Persistent[d] | 157 (76) | 154 (74) | 160 (96) | 151 (61) |
| Unknown | 43 (21) | 50 (24) | 0 (0) | 93 (38) |
| **HPV—digene cervix: *no. (%)*** | | | | |
| Positive | 131 (64) | 130 (62) | 117 (70) | 144 (58) |
| Negative | 57 (28) | 59 (28) | 45 (27) | 71 (29) |
| Unknown | 18 (9) | 20 (10) | 5 (3) | 33 (13) |
| **HPV—digene vagina: *no.* (%)** | | | | |
| Positive | 60 (29) | 55 (26) | 91 (54) | 24 (10) |
| Negative | 23 (11) | 34 (16) | 43 (26) | 14 (6) |
| Unknown | 123 (60) | 120 (57) | 33 (20) | 210 (85) |

CFup, colposcopic follow-up; IT, immediate treatment.
[a] Highest level of education attained.
[b] Income in Canadian dollars.
[c] Incident, all prior smears within 5 years were benign.
[d] Persistent, any prior smears ASCUS or CIN1.

−17.8% to −5.2%) also satisfies noninferiority ($P <$ .001).

A sensitivity analysis was conducted as the primary efficacy analysis because the number of patients dropping out was greater than expected. In the IT arm, the low result of 1.7% with disease progression reflects a best case scenario by assuming that all dropouts did not progress to CIN2/3/cancer. However, in the experimental CFup arm, we over-counted outcomes by applying the observed progression rates to the women lost to follow-up at each follow-up visit. This procedure produced 3 additional "missed" events. Therefore, the sensitivity analysis compared the 1.7% in the IT arm with the 12 of 205 (5.9%) in the CFup arm. This difference (4.2%, 90% CI, 1.0% to 7.8%) also satisfies the noninferiority constraint ($P =$ .017).

Disease progression was only identified in women who were HPV positive at baseline (Table 2).

**Table 2.** HPV Status at Baseline and Patient's Status on Follow-Up

| Group | FUP Visits | HPV Status | n | Disease Progressed |
|---|---|---|---|---|
| IT | [a]Completed | Positive | 74 | 1 |
| | | Negative | 27 | 0 |
| | | Unknown | 9 | 0 |
| | Not completed | Positive | 65 | 2 |
| | | Negative | 11 | 0 |
| | | Unknown | 14 | 0 |
| CFup | [a]Completed | Positive | 90 | 8 |
| | | Negative | 21 | 0 |
| | | Unknown | 15 | 0 |
| | Not completed | Positive | 44 | 2 |
| | | Negative | 9 | 0 |
| | | Unknown | 11 | 0 |
| Total | | | 390 | 13 |

IT, immediate treatment; CFup, colposcopic follow-up.
[a] Completed indicates subject had all 3 visits.

### *Disease Persistence*

In the women who did not develop CIN2/3 or cancer, there were 18 cases of biopsy-proven CIN1 at 18 months: 7 (3.9%) in the IT group and 11 (5.4%) in the CFup group. The 1.4% difference (90% CI, −2.3% to 5.2%) demonstrates a tolerable increase in the rate of persistent biopsy-proven CIN1 at 18 months for those in the CFup arm.

## DISCUSSION

The colposcopist often faces the dilemma of how to manage a patient in the reproductive age group who has a persistent low grade cytology smear, a visible lesion on the cervix, and CIN1 on biopsy. The results of our trial show

that a strategy of colposcopic follow-up with intervention for progression of disease over 18 months is not inferior to IT with LEEP, and reflects the low risk of developing a high-grade lesion with either strategy.

The rate and severity of bleeding complications from LEEP in this trial are in keeping with those reported from other single institution case series.[6] It is too early to assess treatment impact on long-term fecundity.

Our study population consisted of women from Canada and Brazil, 72% aged 30 years or younger, who presented to the colposcopy clinic, 75% of whom had prevalent low-grade dysplasia. The participants in this study reflect the women who attend colposcopy clinics with CIN1 lesions.[15] Thus, our results are generalizable to the Canadian and Brazilian populations and likely to other jurisdictions.

In this study, 31 patients (17.5%) in the IT arm had CIN2/3/cancer at initial LEEP, although the biopsy for eligibility showed CIN1. This number of high-grade lesions in the IT arm is much higher than that seen in the CFup arm over 18 months of assessment. This may reflect resolution of small high-grade lesions over time as a result of the woman's own immune system or as a result of an inflammatory response initiated by the biopsy. It likely reflects the modest sensitivity of colposcopically-directed biopsy to detect the extent of disease. Similarly, cytological confirmation of nonprogression may underestimate the extent of underlying disease. This problem has previously been highlighted where immediate colposcopy of those women recruited to the atypical squamous cells of undetermined significance/low grade intraepithelial lesion triage study (ALTS) detected only 56% of the CIN3 cases identified over 2 years.[13] This has implications for the design of future trials in this patient group, in particular, the assessment of outcomes. One strategy for the assessment of disease burden at 18 months in our trial could have been 4 quadrant biopsies or even LEEP. However, we did not feel LEEP was an ethical option.

At the time this study was carried out, HPV testing was not routinely available for initial screening or follow-up of abnormal cytology results. The specific oncogenic HPV types featured in this study generally reflect the average rates of specific oncogenic HPV seen in the North and South American results reported by Clifford.[14] In our study, the exceptions were higher rates of HPV-52 and HPV-53 and the lack of HPV-66. The only patients who progressed in this study were HPV positive. This suggests that women who are HPV negative could revert to routine screening. Those who are HPV positive require closer surveillance.

Our trial had several limitations. First, we did not reach the targeted sample size. Despite attempts to enlist more centers and expand to other countries, recruitment was discontinued when the funding agency terminated support. The screening logs suggested there were many reasons for the lower than anticipated recruitment. At the time this study was conducted, it was uncommon to do multicenter trials in Canadian colposcopy clinics. At some sites there was low investigator motivation (eg, nontimely completion of regulatory paperwork, poor communication with the colposcopy clinic staff). The site-specific issues included access to clinical trials staff and a trials infrastructure. Patient factors included personal preference for a management strategy, desire for fertility now, unwillingness or geographic inability to participate in follow-up. International issues included language barriers, completion of regulatory documents, and transport of temperature-sensitive specimens.

The second major limitation was the number of patients who were lost to follow-up. This made the analysis complicated. Patients were lost after randomization, after LEEP, and during the 18-month follow-up period. More patients were lost in the CFup arm. It is possible that if some of these patients had higher-grade disease, the conclusion of noninferiority would no longer hold. However, we performed a sensitivity analysis that reflected our best estimate of high-grade disease in patients lost to follow-up. By using such an approach, the conservative strategy of colposcopic follow-up with intervention only at progression remained noninferior.

Noncompliance with follow-up is well documented in the literature with rates of 26% to 56% reported.[15] It is of interest that, in 1 study, compliance was directly related to socioeconomic class.[16] Follow-up was more of an issue in Brazil, where child care and transportation to and from the clinic were costly relative to income.

The only other clinical trial that addressed the use of LEEP or biopsy as the best management of women with borderline or low-grade abnormal smears is the TOMBOLA trial.[17,18] This study included different populations and used different strategies, and, therefore, is not directly comparable to our study.

In the 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia,[19] the recommended management for a histologic diagnosis of CIN1—preceded by prevalent cytology of LSIL or less—is cytology every 6 to 12 months with colposcopy.

This strategy, devised from evidence from cohort studies, is now further supported by the results of our randomized trial.

## CONFLICT OF INTEREST DISCLOSURES

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