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Rate of and Risks for Regression of CIN-2 in adolescents and young women

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Abstract

Objective—To describe the natural history of CIN-2 in a prospective study of young women and to examine the behavioral and biologic factors associated with regression and progression.

Methods—Women aged 13 to 24 years referred for abnormal cytology and were found to have CIN-2 on histology were followed at 4-month intervals. Risks for regression defined as 3 consecutive negative cytology and histology visits and progression to CIN-3 were estimated using Cox proportional hazards regression models.

Findings—Ninety-five women with a mean age of 20.4 years (± 2.3) were entered into the analysis. Thirty-eight percent cleared by year 1, 63% by year 2 and 68% by year 3. Multivariable analysis found that recent *N. gonorrhoeae* infection (H.R. = 25.27 [95% C.I. 3.11, 205.42]) and medroxyprogesterone acetate use (per month) (H.R. = 1.02 [95% C.I. 1.003, 1.04]) were associated with regression. Factors associated with non-regression included combined hormonal contraception use (per month) (H.R. = 0.85 [95% C.I. 0.75, 0.97]) and persistence of HPV of any type (H.R. = 0.40 [95% C.I. 0.22, 0.72]). Fifteen percent of women showed progression by year 3. HPV 16/18 persistence (H.R. = 25.27 [95% C.I. 2.65, 241.2, $p = 0.005$]) and HPV 16/18 status at last visit (H.R. = 7.25 [95% C.I. 1.07, 49.36]; $p < 0.05$) was associated with progression. Because of the small sample size, other co-variates were not examined.

Conclusion—The high regression rate of CIN-2 supports clinical observation of this lesion in young women.

Introduction

Cervical intra-epithelial lesions (CIN) and cervical cancers are caused by human papillomavirus (HPV). CIN-1 is a histologic diagnosis associated with benign viral replication and in most cases spontaneously regresses. (1–3) Studies in adult women show

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regression rates of 70–80% whereas in adolescents and young women, over 90% show regression. (1–4) Because of these high regression rates, it is recommended in the U.S. that clinicians manage conservatively with observation, rather than treat, CIN-1 in adolescents. (5)

In contrast, CIN-3 is considered a true precancer with the potential to progress to invasive cancer at the rate of 0.2% to 4% within 12 months. (6) The biologic behavior of CIN-2 is more controversial. Many clinicians consider CIN-2 a precancerous lesion and therefore, routinely treat these lesions. (5) The annual regression rate of CIN-2 in adult women is estimated to range from 15 to 23%, with up to 55% regressing by 4–6 years. (3,7,8) As with CIN-1, data in adolescents suggest that CIN-2 has a much higher likelihood of regression. In a chart review of 23 patients, Moore et al (9) observed a regression rate of 65% while 13% progressed to CIN-3. In a database review, Fuchs et al (10) reported that 39% of adolescents with untreated CIN-2 showed regression to normal with 92% showing CIN-1 or less after 3 years. Only 8% had CIN-2 persistence or progression. Certainly rates of cervical cancer are low in adolescents and young women supporting that progression of CIN-2 to cancer in this age group is extremely rare. (11)

The purpose of this paper is to describe the natural history of CIN-2 in a prospective study of women aged 13 to 24 years of age and to examine behavioral and biologic factors associated with regression and progression.

Material and Methods

Women aged 13 to 24 years of age who had abnormal cervical cytologic screening showing atypical squamous cells of undetermined significance (ASC-US), low grade squamous intra-epithelial lesion (LSIL) or high grade squamous intra-epithelial lesion (HSIL) while attending one of the 12 participating clinics within Kaiser Permanente, Northern California (KPNC) were eligible for recruitment. Details of the recruitment have been reported elsewhere. (12) Exclusion criteria included previous treatment for CIN, immunosuppression, pregnancy or planning to leave the area within 3 years. This study was approved by both the institutional review boards of the University of California, San Francisco (UCSF) and KPNC. At the time this study was initiated in 2002, ASC-US/HR (high risk HPV positive), repeat ASC-US, LSIL and HSIL were all immediately referred to colposcopy. Recruitment was completed in 2007. Eighty percent of those who were contacted agreed to participate. Data is unavailable on women who were never contacted or refused to participate. At baseline and each 4 month follow-up visit, charts were reviewed to verify all reported STIs and a face-to-face interview was conducted to obtain behavioral data. The following were obtained at each visit: a vaginal sample for bacterial vaginosis (13) and wet mount for yeast and *T. vaginalis*; cervical sample for cytology and HPV and for *N. gonorrhoeae* (NG) and *C. trachomatis* (CT) at the annual visit or if symptomatic. Biopsies performed at baseline were sent to each of the respective KPNC site pathology laboratory and then released for a second review by a single pathologist (T. Darragh, UCSF). CIN-3 diagnosis were confirmed by a third pathologist. (12) Patients with a diagnosis of CIN-2 by either UCSF or KPNC were allowed into the follow-up study. If CIN-3 was diagnosed at either site, the subject was exited. (12) All study cytology and histology samples during follow-up were sent to the centralized laboratory to be reviewed by a single pathologist (T. Darragh). During follow-up, women underwent biopsy if the colposcopist was concerned about progression or if the cytology on any visit suggested progression. At the end of the study, all participants were asked to consent to a cervical biopsy, regardless of cytologic diagnosis or colposcopic impression. If no colposcopic abnormality was noted on this final visit, the site of initial CIN-2 was targeted for biopsy. Not all women underwent biopsy at the end because either they refused or did not come in for the final visit.

Samples for cytology and HPV were immediately placed into liquid based media (PreservCyt; Hologic Corp, Marlborough, MA) and were sent to the UCSF laboratory where 9 mL was removed for amplification and genotyping. (12,14) All HPV testing used the Roche Linear Array Assay (Roche Molecular Diagnostics, In, Alameda, CA) testing for HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, and 89.

Data analysis

Only women with at least two visits (baseline and at least one follow-up visit) were considered for this analysis. Definition of progression was biopsy proven CIN-3 at any visit after the baseline determination of CIN-2. Definition of regression was based on having three consecutive visits with negative cytology, and negative biopsy on any of these visits, if available. If there was insufficient follow-up (i.e. only one visit with negative cytology), the analysis was censored at the last visit with abnormal cytology or histology. If the subject continued to have LSIL or HSIL on cytology or CIN-1 or 2 on histology at end of follow-up, she was considered to be a non-regressor (i.e. persistent). Histologic diagnosis, if available, was used for the analysis over a negative cytologic diagnosis at any visit.

To compare the socio-demographics between participants and those with no follow-up data (non-participants), we used t-tests for continuous variables, and χ^2 test or two-tailed Fisher's exact test for categorical variables, when appropriate. Kaplan-Meier estimates of time to CIN-2 regression or progression were based on the date of CIN-2 detection and the first of 3 consecutive visits with normal cytology or the first CIN-3 diagnosis. Once an event was reached, the remaining visits were censored from the analysis. The comparisons between Kaplan-Meier curves were based on log-rank test. The independent variables included both fixed and time-dependent covariates and their effects on CIN regression or progression were estimated in Cox proportional hazards regression models. When variables of similar characteristics were significant in univariable models (i.e. HPV persistence), we entered each of them in a separate multivariable model to avoid potential colinearity problems. For the CIN-2 regression analysis, the variables that were significant at $p \leq 0.05$ level in univariable models were considered in the multivariable regression models. No significant violations of the proportional hazards assumption were detected for fitted regression models. We also performed a sensitivity analysis for those CIN-2 cases confirmed by a second pathologist. For the analysis for progression to CIN-3, the multivariable analysis was severely limited because of the small number of women who progressed. We focused on the most biologically plausible variable, HPV status. We performed a regression analysis for each of the 4 HPV variables (HPV persistence of any type, HPV 16/18 persistence, HPV 16/18 status at entry and at last visit). Each of analysis adjusted for the other variables found to have a p value <0.1 in the univariable analysis.

Results

Of the 715 women screened, 120 met criteria for CIN-2 follow-up at the baseline visit. Twenty-five women had no follow-up visit because they either verbally refused to enter the CIN-2 follow-up study or did not return for follow-up. Consequently, 95 women agreed to participate and had at least two visits (baseline and first follow-up). The demographics of these 95 women are given in Table 1. There were no statistical differences for these demographic characteristics between those who participated and those who did not return (Table 1). Forty-eight women were diagnosed with CIN-2 by both UCSF and KPNC pathologists. Forty-two women had discordant diagnosis (i.e. one of the diagnosis was less than CIN-2)-16 women had CIN-2 by KPNC and 26 by UCSF. Five women with CIN-2 were evaluated only by UCSF. Mean period of observation was 27.4 months (SD 11.6) with

a range of 3.8 to 46.8 months. Sixty five (68%) of women had an exit biopsy. Median number of biopsies during follow-up was 1 (range 0 to 6).

Time to clearance of CIN-2

Time to clearance for the 95 women with CIN-2 is shown in figure 1. Thirty-eight percent (95% C.I. 29, 49%) of women with CIN-2 cleared by 1 year, 63% (95% C.I. 53, 74%) by 2 years and 68% (95% C.I. 57, 78%) by 3 years. Time to clearance by HPV 16/18 baseline status is shown in Figure 2. Of those with HPV 16/18 ($n = 42$), 31.6% (95% C.I. 20, 48%) showed clearance by 1 year, 44.1% (95% C.I. 30, 62%) by 2 years and 55.1% (95% C.I. 39–72%) by 3 years. In comparison, among women with non-HPV 16/18 CIN-2, 43.7 % (95% C.I. 31, 59%) showed clearance at 1 year ($p = 0.27$), 78% (95% C.I. 65, 89%) at 2 years ($p = 0.01$) and 78% (95% C.I. 65, 89%) at 3 years ($p = 0.03$). No difference in time to clearance was found if the CIN-2 diagnosis was concordant between the KPNC and UCSF pathologists vs discordant (Figure 3 [$p = 0.75$]).

Closer examination of the 42 women with HPV 16/18 showed that 20 women with HPV 16/18 immediately cleared their HPV 16 (i.e. they had a single positive HPV 16 DNA test). Of these, 18 (90%, 95% C.I. 76.9, 100%) cleared their CIN-2 and 2 had CIN-2 persistence. These 2 patients also had infection with other HPV types: one was persistently positive for HPV 52, the other was positive for HPV 18 and 31 at baseline, 2nd visit had HPV 18 and 61, 3rd visit had HPV 61, 4th and last visit had HPV 51. Of the 22 women with HPV 16/18 persistence, defined by at least two positive HPV 16 tests over the observed period (persistence ranged from 4 months to 26 months), 8 (36.4%, 95% C.I. 16.3, 56.5%) had progression to CIN-3, 11 (50%, 95% C.I. 29.1, 70.9%) had regression, and 3 (13.6%, 95% C.I. 2.9, 34.9%) had regression to CIN-1.

The appearance of new HPV types over the observed period was extremely common with 84 (88.4%, 95% C.I. 82, 94.9%) women acquiring new HPV types. In addition to the 15 women who progressed or persisted, 17 (44.7%, 95% C.I. 28.6, 61.7%) women were considered non-regressors because they had CIN-1 at the end. Of these 17 women, 8 (47.1%, 95% C.I. 23.3, 70.8%) had HPV persistence of the type found at the baseline CIN-2 visit, and 9 (52.9%, 95% C.I. 29.2, 76.7%) had a new HPV type with clearance of the initial HPV type. Six women were found to have only two consecutive visits with normal cytology before lost to follow-up. Of these 6, 4 (67%, 95% C.I. 22.3, 95.7%) had cleared the HPV observed at the CIN-2 visit and 2 (33%, 95% C.I. 4.3, 77.7%) had persistence of that type.

Factors associated with CIN-2 regression

Table 2 shows the univariable associations with CIN-2 regression. Factors associated with regression at the $p < .05$ level included older age at first intercourse, a recent reported infection with *N. gonorrhoeae*, months on medroxyprogesterone acetate. Factors associated with non-regression included greater number of months of combined hormonal contraception use, HPV persistence, HPV 16/18 persistence, HPV 16/18 infection status at baseline and at last visit. Because the HPV variables were highly correlated, multivariable models were run for each HPV variable separately. In the 4 multivariable models, all the variables remained significant except for HPV 16/18 status at entry which became marginally significant. All the biologic and behavioral variables had similar H.R. as presented in Table 3. The results are summarized in Table 3. The sensitivity analysis for the CIN-2 cases which were confirmed by a second pathologist showed similar results as presented in Tables 2 and 3 (data not shown).

Progression to CIN-3

Time to progression to CIN-3 is shown in Figure 4. Two percent (95% C.I. 1, 9%) of women showed progression to CIN-3 by year 1, 12% (95% C.I. 8, 22%) by year 2, and 15% (95% C.I. 9, 26%) by year 3. No cases of cervical cancer occurred during follow-up. Of the 11 women who progressed, 8 were positive for HPV 16, 1 for HPV 51, 1 for HPV 31, and 1 for HPV 51, 52, and 58 at the CIN-3 visit.

Factors associated with progression to CIN-3

In the univariable analysis factors associated with progression to CIN-3 at the $p < 0.1$ level are summarized in Table 4. All the HPV variables (HPV persistence of any type, HPV persistence of HPV 16/18, HPV 16/18 status at entry and last visit) were significantly associated with progression. In addition, young age of menarche, history of reported douching since the last visit, weekly alcohol use, engaging in anal sex, and having a history of genital warts were associated with progression. The small number of cases that progressed precluded us from performing any meaningful full multivariable model. Hence we focused the analysis on the HPV variables. After adjusting for the 5 potentially confounding variables, HPV 16/18 persistence (H.R.=25.27 (95% C.I. 2.65, 241.2; $p=0.005$) and HPV 16/18 status at last visit (H.R.=7.25 (95% C.I. 1.07, 49.36; $p < 0.05$) remained significant whereas HPV persistence of any type (H.R. was not calculable; $p=0.99$) and HPV 16/18 status at entry (H.R.=2.87 (95% C.I. 0.48, 17.06); $p=0.25$) were no longer significant. Of note, young, age of menarche remained significantly associated ($p \leq 0.05$) with progression in all 4 models. The lowest H.R. was for the model with HPV 16/18 persistence (H.R. = 0.36 (95% C.I. 0.13, 1.0; $p = 0.05$) and the highest H.R. was for the model with HPV persistence (H.R. = 0.44 (95% C.I. .021, 0.92; $p = 0.03$). All the other variables were either not significant or inconsistently significant.

Discussion

In this prospective study of CIN-2 in adolescents and young women, regression of CIN-2 was common with almost 70% regressing to normal within 3 years. To be conservative, we classified those with CIN-1 at the last visit as non-regressors. Since many of the CIN-1 lesions appeared to be associated with new HPV types, the regression rate of CIN-2 is likely even higher. However, we note that few showed regression after two years of follow-up. In the similar vein, progression to CIN-3 was not common in the 1–2 years following the CIN-2 diagnosis. This data supports the 2006 ASCCP Consensus Guidelines recommendation for observation for up to two years for adolescents and young adult women with CIN-2. (5) These rates of regression are higher than those reported in previous prospective studies and are likely due to the younger age of our cohort. Younger age likely reflects a shorter time of HPV persistence at entry into study. The association found in our study between older age of first intercourse and regression underscores this premise. Syrjanen et al (3) reported a CIN-2 regression rate of 53% and a progression rate of 21%. Their study had several differences in that women were older and not all women in the study had confirmation of CIN-2 by biopsy. This group also reported regression and progression rates for those with CIN-2 confirmation and reported that 24 of 70 (34%) with CIN-2 regressed and 14 (20%) progressed. (15) Another older study by Nasiell et al (2) also showed a lower regression rate of 54% with a progression rate of 30%. This study used cytology as the sole entry diagnosis and included older women ranging from 15 years to 72 years. The relevance of most of these studies to young women today is unclear since sexual behavior, contraceptive use, and smoking habits have all changed since most of these cohort studies were performed. Although not prospective studies, two more recent studies by Moore et al (9) and Fuchs et al (10) had estimates similar to ours.

Although the rate of regression was high, it was lower than that reported for CIN-1 (4) and higher than that reported for CIN-3. (6) This suggests that CIN-2 may have some distinct biologic characteristics or the morphologic classification may not accurately reflect the biologic potential. Some have argued that CIN-2 as a lesion does not exist. Most agree that the reproducibility of a histologic diagnosis of CIN-2 is poor as shown in our study (7,16) Interestingly, concordance of diagnosis did not influence the regression rate.

Not surprisingly, HPV persistence was a factor associated with non-regression - as found in many other studies. (17) In comparison, HPV 16/18 status at entry was not significant underscoring the high rate of HPV 16/18 clearance seen in most young women. These observations warrant further clinical studies that examine the potential use of HPV DNA testing in follow-up of CIN-2. The finding associated with hormonal contraception and CIN-2 persistence was also not surprising since its use has been associated with the development of CIN-3 and invasive cervical cancer. (18) We previously reported on risk factors from the baseline visit of this study associated with CIN-3. (12) In that report, one of the risks was time on combined oral contraceptives (OC). (12) This finding may suggest that the mechanism by which oral contraceptives play a role is by assisting in the transcription of viral oncoproteins that result in the histologic changes of CIN-2. (19) Interestingly, progesterone only contraceptives seem to assist in clearance. This finding is incongruous with the literature that show medroxyprogesterone acetate and combined OC are associated with cancer. (20)

Interpreting the observation that infections with *N. gonorrhoeae* assisted in regression is limited because of the few cases that occurred. We hypothesize that the intense inflammatory response induced by *N. gonorrhoeae* infections may have serendipitously assisted in viral clearance.

Since few women in this study progressed to CIN-3, as expected in this young population, our findings regarding risks for progression have serious limitations. The wide confidence intervals underscore the potential instability of the variables. As expected, we found that HPV 16/18 persistence was a risk for progression with an almost 20 fold risk of progression over the observed period. Although there were wide confidence intervals, the association remained relatively stable even after adjusting for numerous potential confounders. It is difficult to comment on the persistence of other HPV types since HPV 16/18 predominated this analysis. In comparison, single point HPV 16/18 testing appeared less informative. Although we focused the analysis on the HPV variables, we observed that the association with young age of menarche appeared relatively stable in all the models. This is interesting since other gynecologic cancers including ovarian and endometrial have been associated with young age at menarche. (21–23) Young age of menarche is thought to reflect a higher cumulative exposure to estrogen. This would be consistent with our findings associated with OC use and CIN-2 persistence and OC use and CIN-3 in the cross-sectional baseline analysis. The lack of finding an association with OC use in this study may have been due to the small number of CIN-3 cases or that the influence associated with OC use targets viral persistence and not mutational events that result in CIN-3.

In summary, our data show that CIN-2 commonly regresses spontaneously in young women supporting the conservative approach in observing young women with CIN-2. Factors associated with CIN-2 regression and progression to CIN-3 were correlated with HPV persistence, specifically HPV 16/18 infections. The findings with combined hormonal contraceptive use and age at menarche support the premise that reproductive hormones are important influences on persistence and progression.

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Figure 1.
Time to clearance of CIN-2

Figure 2.
Time to clearance of CIN-2 by HPV 16/18 status

Figure 3. Time to regression of CIN-2 by concordance status. Concordance was agreement of CIN-2 between 2 pathologists. Disagreement was when one pathologist gave a diagnosis of CIN-1 or less

Figure 4.
Time to progression of CIN-2 to CIN-3

Table 1

Demographics and Behavioral Characteristics of the Population at Baseline N = 95 participants, 25 non-participants

Characteristics	Participants N (%)	Non-Participants N (%)	p-value*
Race (N %)			0.72
White	40 (42.1)	11 (44.0)	
Black	25 (26.3)	9 (36.0)	
Asian	7 (7.4)	0 (0)	
Hispanic	19 (20.0)	4 (16.0)	
Mixed/other	4 (4.2)	1 (4.0)	
History of reported genital warts	11 (11.6)	2 (8.3)	0.65
History of reported <i>C. trachomatis</i>	30 (31.6)	9 (37.5)	0.58
History of reported <i>N. gonorrhoeae</i>	4 (4.2)	1 (4.2)	1.0
History of reported STI, but can't remember the name	2 (2.1)	0 (0)	1.0
Currently smokes cigarettes	27 (36.5)	8 (38.1)	0.89
Weekly alcohol use	2 (2.1)	0 (0)	1.0
Weekly marijuana use	15 (15.8)	3 (12.0)	0.76
Weekly drug use	0 (0)	1 (4.0)	0.21
Condom use during last sexual intercourse	23 (32.4)	9 (52.9)	0.11
History of anal sex	13 (13.8)	4 (16.0)	0.78
Ever Pregnant	41(43.2)	9 (37.5)	0.62
Ever used hormone contraception	65 (68.4)	16 (64.0)	0.67
Ever used medroxyprogesterone contraception	37 (38.9)	13 (52.0)	0.24
	Mean (±S. D.)	Mean (±S. D.)	
Mean Age (years)	20.4 (± 2.3)	20.2 (± 1.9)	0.66
Mean age at menarche (years)	12.8 (± 1.5)	12.8 (± 1.7)	0.93
Mean age at 1 st sexual intercourse (years)	15.6 (± 2.5)	16.3 (± 1.5)	0.16
Number of lifetime sexual partners	7.9 (± 6.7)	6.0 (± 4.4)	0.10

Table 2

Univariable analysis for risk of CIN-2 regression

Independent variable	Hazard Ratio (95% CI)	p-value
Age	1.09 (0.97, 1.23)	0.16
Age at first sex	1.18 (1.03, 1.35)	0.02
Age at menarche	1.07 (0.90, 1.28)	0.43
Black	0.78 (0.41, 1.49)	0.45
Latina	0.68 (0.33, 1.41)	0.30
Other race	0.96 (0.41, 2.21)	0.92
Douched since last visit	1.57 (0.66, 3.70)	0.26
Smoking last 24 hours	1.50 (0.79, 2.86)	0.22
Weekly alcohol use	1.62 (0.78, 3.36)	0.19
Weekly marijuana use	0.47 (0.19, 1.19)	0.11
Weekly drug use	3.79 (0.49, 29.50)	0.20
Condom use since last visit	1.28 (0.74, 2.21)	0.38
Irregular menstrual cycles	1.60 (0.58, 4.52)	0.36
Current pregnancy	0.59 (0.18, 1.91)	0.38
History of pregnancy	1.07 (0.63, 1.81)	0.81
Engaged in anal sex since last visit	0.56 (0.20, 1.55)	0.26
Reported BV since last visit	1.11 (0.47, 2.63)	0.81
Reported <i>N. gonorrhoeae</i> since last visit	15.61 (2.87, 84.76)	0.001
Reported <i>T. vaginalis</i> since last visit	0.64 (0.09, 4.73)	0.66
Reported <i>C. trachomatis</i> since last visit	1.26 (0.50, 3.17)	0.63
Reported unknown STI since last visit	1.37 (0.61, 3.06)	0.44
History of unknown STI since last visit	0.88 (0.42, 1.82)	0.73
Genital warts since last visit	0.68 (0.16, 2.82)	0.59
Yeast infection since last visit	0.97 (0.52, 1.78)	0.91
Combined hormonal contraception (per month of use)	0.86 (0.75, 0.97)	0.02
Medroxyprogesterone (per month of use)	1.01 (1, 1.03)	0.05
Current use of combined hormonal contraception	0.70 (0.39, 1.26)	0.24
Current use of medroxyprogesterone	1.09 (0.51, 2.33)	0.83
New sexual partners since last 2 visits	0.99 (0.75, 1.31)	0.97
Total number of sexual partners per month *	0.08 (0.01, 1.32)	0.08
Currently sexual abstinence	1.1 (0.62, 1.97)	0.85
HPV persistence	0.31 (0.17, 0.55)	<0.0001
HPV 16/18 persistence	0.11 (0.03, 0.46)	0.002
HPV 16/18 at last visit	0.21 (0.08, 0.53)	0.001
HPV 16/18 at entry visit	0.54 (0.31, 0.93)	0.03

* Reflects total number of lifetime partners divided by the number of months sexually active

Table 3

Multivariable* analysis for risk of CIN-2 regression

<u>Independent variable</u>	<u>Hazard Ratio (95% C.I.)</u>	<u>p-value</u>
Age of 1 st intercourse (per year)	1.25 (1.06, 1.48)	0.009
Reported <i>N. gonorrhoeae</i> since last visit	25.27 (3.11, 205.42)	0.003
Combined hormonal contraception use (per month of use)	0.85 (0.75, 0.97)	0.02
Medroxyprogesterone acetate use (per month of use)	1.02 (1.003, 1.04)	0.02
HPV persistence**	0.40 (0.22, 0.72)	0.002

* Variables found significant at $p \leq 0.05$ level in the univariable analysis were considered for the multivariable analysis.

** If variable was replaced by HPV 16/18 persistence, H.R.= 0.24 (95% C.I. 0.07, 0.85), $p=0.03$; if replaced by HPV 16/18 status at last visit, H.R.=0.36 (95% C.I. 0.15, 0.87), $p=0.02$ if replaced by HPV 16/18 at entry, H.R.=0.59 (95% C.I. 0.10, 1.10), $p=0.10$. The significance of the other variables remained similar in all 3 models.

Table 4

Univariable analysis for risk of CIN-2 progression to CIN-3

<u>Independent variable</u>	<u>Hazard Ratio (95% C.I.)</u>	<u>p-value</u>
Age at menarche	0.57 (0.35, 0.94)	0.03
Douched since last visit	5.54 (1.05, 29.16)	0.04
Weekly alcohol use	4.75 (1.05, 21.46)	0.04
Ever engaged in anal sex	3.51 (0.81, 15.15)	0.09
History of genital warts	5.26 (1.48, 18.71)	0.01
HPV 16/18 at entry visit	6.6 (1.42, 30.62)	0.02
HPV persistence of any type	27.04 (3.4, 214.9)	0.001
HPV 16/18 persistence	19.98 (5.07, 78.82)	<0.0001
HPV 16/18 at last visit	8.74 (2.31, 33.07)	0.001

* Only variables found significant at $p < 0.1$ are shown.