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# Persistence and Progression of Low-grade Cervical Intraepithelial Neoplasia 1 by Combination of Cervical Cytology and HPV mRNA Testing: a Three-Year Follow-Up

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**ABSTRACT**

This study aimed to gather the persistence and progression rates of histologically confirmed cervical intraepithelial neoplasia 1 (CIN 1) and the three-year follow-up data using a combination of liquid-based cytology and human papillomavirus messenger RNA (HPV mRNA) methods in order to evaluate the current American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for suitability and practicality when applied to the local Thai population. A retrospective cohort study was conducted at Thammasat University Hospital (TUH) with data collected from October 2013 to September 2016. All cases that indicated colposcopy underwent colposcopic directed biopsy. CIN 1 cases were enrolled and followed up on for three years. Persistence and progression rates of CIN 1 were evaluated. During the study period, data from 383 cases of patients who underwent CDB were enrolled in this study. One hundred and thirty-four cases with cervical-histologically confirmed CIN 1 were analyzed for up to three years. The mean age of participants was 46.6 years. One-third of the participants were in menopause. Two-thirds had a history of sexually transmitted diseases (STDs). Only one-fifth of participants had been vaccinated for HPV. The cumulative incidence rate of CIN 3+ at three years, the persistence rate, and the regression rate of CIN 1 were 4.53, 9.4, and 87.5 percent, respectively. In conclusion, CIN 1 cases should be treated more aggressively and monitored frequently in Thai populations due to the higher incidence of CIN 3.

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**Keywords:** CIN 1; Cumulative CIN 3+ rate; Low grade cytology; HPV mRNA; HPV

## 1. Introduction

Cervical cancer is the 2nd most common cancer among Thai women, with 9,158 new cases (age-standardized incidence rate is 16.4 persons per 100,000 women per year) and 4,705 deaths annually [1]. High-risk human papillomavirus (hrHPV) is the causative pathogen for cervical cancer. The Thai government's cervical cancer management strategy is to offer a combination of hrHPV testing with cervical cytology (co-testing) or primary hrHPV testing without cytology (stand-alone HPV test). However, co-testing has been recommended for CIN follow-up care during the first or/and second years [2].

According to the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) risk-based management protocols, colposcopy referral thresholds are set for immediate risk of CIN 3+ equal to or greater than 4 percent [2]. ASCCP guidelines are based on countries with either a lower incidence of cervical cancer or countries with higher affluence [3]. However, countries with higher incidence rates of cervical cancer are known to report a higher immediate rate of CIN 3+ in low-grade cervical cytology [4]. These findings underscore the need for definitive research to be undertaken to evaluate the applicability and practicality of implementing ASCCP guidelines in Thailand, where a higher incidence rate of cervical cancer is reported [5].

This study aimed to investigate the rate of persistence and cumulative CIN 3+ among CIN 1 lesions within 3-years of testing.

## 2. Materials and Methods

### 2.1 Study design, location, and population

A retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine (FOM), Thammasat University Hospital (TUH). The study was approved by the FOM TUH ethics committee on clinical research (MTU-EC-OB-1-163/62). The study was supported by the FOM, Thammasat University Research Fund, Contract No. 2-02/2564. Data were collected and reviewed from cases that underwent colposcopy between October 2013 and September 2016 at TUH. All cases indicating colposcopy underwent colposcopic directed biopsy [6]. Participants who did not follow up or were previously diagnosed with cervical cancer, pre-invasive cervical lesions, or had undergone hysterectomies from other gynecologic cancers were excluded from the study. CIN 1 histology proven by cervical biopsy under colposcopy or loop electrosurgical excision procedure (LEEP) were enrolled and had their follow-up data analyzed up to three years post-treatment.

### 2.2 Research tools

At TUH, an hrHPV mRNA assay (APTIMA®HPV; Hologic, CA, USA) has been routinely used since 2013. The hrHPV mRNA-based testing, when compared to DNA-based testing, shows similar sensitivity and higher specificity in detecting CIN 2+ [7]. Information pertaining to cytology, hrHPV status, colposcopic examination, and histology report was recorded from electronic medical records and reviewed. Additional data on age, parity, menopausal status, HPV vaccination status, number of sexual partners, and history of sexually transmitted diseases (STDs) were also collected.

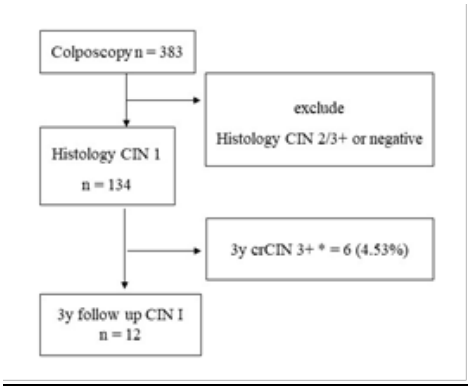
### 2.3 Data analysis

Descriptive statistics was used to describe demographic data. Continuous data are presented as mean and standard deviation. The cumulative incidence was calculated by using life table statistics, proportional, and Clopper-Pearson's exact confidence interval. All analyses were

carried out using SPSS Statistics version 18 (SPSS Inc., Chicago, USA).

## 3. Results and Discussion

During the study period, data from 383 cases of patients who underwent colposcopy-directed biopsy were collected. A total of 249 cases were excluded due to their CIN 2/3+ presentation and other criteria. A total of 134 cases of confirmed CIN 1 cervical histology were recruited, reviewed, and the corresponding follow-up data for three years were analyzed as shown in Fig. 1.




*n (%),3y crCIN 3+: 3-year cumulative incidence rate of CIN 3+, CIN: cervical intraepithelial neoplasia

**Fig. 1.** Flow chart of the study.

The mean age of participants was 46.6 years. One-third of the participants had undergone menopause. Half of the participants were multiparous. Two-thirds had a history of STDs. A quarter had prior experience with contraception or had experienced unsatisfactory colposcopies. Only one-fifth of participants had HPV vaccination prior to presentation. Percentages of hrHPV type 16/18, and non-16/18, as detected by mRNA technique, were 17.2 and 23.9, respectively as detailed in Table 1. The colposcopists in this study had experience ranging from 5-20 years.

From demographic data, the cytologic abnormality for each participant was collected and correlated with population characteristics. HSIL, ASC-H, LSIL, ASC-US, and NILM were reported at 3, 1.5, 16.4, 9.7, and 69.4 percent, respectively.

**Table 1.** Demographic data of enrolled cases during the study period.

| | CIN 1 ($n$ = 134) * |
|---|---|
| Age (year)** | 46.6±11.3 |
| Menopause | 47 (35.1) |
| Multiparity | 60 (44.8) |
| Polygamy | 56 (41.8) |
| STDs | 82 (64.2) |
| HIV infection | 9 (6.7) |
| Vaccination | 28 (20.9) |
| Contraception | |
| Barrier method | 20 (14.9) |
| hormonal | 17 (12.7) |
| Specimen adequacy [t] | 81 (60.4) |
| Unsatisfactory colposcopy | 52 (23.8) |
| hrHPV | |
| 16/18 | 23 (17.2) |
| non-16/18 | 32 (23.9) |

*$n$ (%), **mean ± SD (standard deviation), CIN 1: Cervical Intraepithelial Neoplasia Grade 1, STDs: sexually transmitted diseases, HIV: human immunodeficiency virus, Vaccination: bivalent or quadrivalent of human papillomavirus vaccine, t: present transformation zone on preceding cytology, hrHPV: High-risk human papillomavirus

During the study period, CIN 2 and CIN 3 were diagnosed in 6 and 6 cases, respectively. All underwent the LEEP procedure. All cervical conization histology was relevant to the colposcopic biopsy reports. All who persisted with CIN 1 during the follow-up period ($n$ = 12) underwent cervical cryotherapy via the double freezing technique.

The three-year persistence and regression rates of CIN 1 were 9.4 and 87.5 percent, respectively. Cases with progression to the higher severity CIN 3 were reported as the cumulative incidence rate of CIN 3+ (crCIN 3+). The crCIN 3+ results at one, two and three years of follow-up were 2.24, 4.53, and 4.53 percent, respectively (Table 2). The

cumulative proportion of CIN 1 during the follow-up period is presented in Fig. 2. The persistence rate of CIN 1 at one and two years was 0.16 and 0.12, respectively.

**Table 2.** Cervical histology of CIN 1 cases during time follow-up (*n*=134).

| Year | Histology(n) | | | | |
|---|---|---|---|---|---|
| | CIN 1 | CIN 2 | CIN 3 | crCIN3+ * | 95% CI |
| 0 | 134 | 0 | 0 | | |
| 1 | 18 | 1 | 3 | 2.24 | (0.00, 4.74) |
| 2 | 10 | 1 | 3 | 4.53 | (0.99, 8.06) |
| 3 | 12 | 4 | 0 | 4.53 | (0.98, 8.08) |

Year: year of follow up during the study, CIN: cervical intraepithelial neoplasia, crCIN3+: Cumulative incidence rate of CIN3+, *%, 95% CI: 95% Confidence Interval
CIN: cervical intraepithelial neoplasia

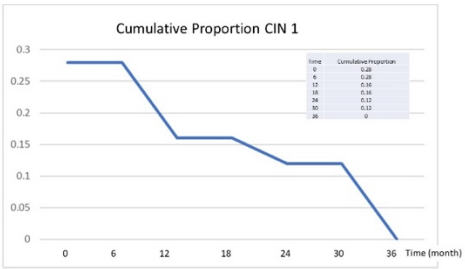



**Fig. 2.** Cumulative Proportion of CIN1.

CIN 1 is a lesion with a low potential of malignancy and typically results in spontaneous resolution [6]. According to ASCCP 2012, post-colposcopy management of CIN 1 depends on the preceding cervical cytology [6]. In cases of CIN 1 with suspicion of CIN 2+, the follow-up period consisted of co-testing for one year. The re-evaluation period was between three and five years according to routine screening procedures and consisted of cytology and/or HPV testing. However, if either cytology or HPV testing yielded abnormal results, an immediate colposcopy is recommended. Further management of abnormal cytology without HPV testing would indicate immediate colposcopy or other diagnostic procedures [6].

According to ASCCP 2019 guidelines, a more conservative approach to follow-up is preferred, as opposed to performing any diagnostic testing such as colposcopy in cases of abnormal cytology or HPV testing [8, 9]. Colposcopy is only considered in cases of high-grade cytology or HPV positive type 16/18 according to immediate CIN 3+ risk.

Participants with CIN I histology would have different follow-up intervals as indicated by ASCCP guidelines, depending on their preceding cervical cytologic abnormality. In our practice, this caused some emotional distress in participants. They saw that other participants with similar diagnoses (CIN I) were re-examined on a different schedule. To counteract this distressing factor, TUH established a more frequent follow-up schedule for all CIN 1 patients than was recommended by the ASCCP guidelines.

While abiding by ASCCP guidelines, our study results indicated that the remission rate of participants with CIN 1 was 87.5 percent at three years. Results were consistent with that of Ciavattini's and Nogara's work, while Loopik's work reported lower remission rates compared to this study [10-12]. Although, Ciavattini's work, conducted in Italy, showed a significantly lower cumulative conversion rate to CIN 2/3+ when compared to this study. However, Zheng's work reported a remission rate for CIN 1 of only 14.9 percent at six months [13].

In this study population, the cumulative incidence rate to CIN 3+ histologic results were 2.24 and 4.53 percent at the one- and two-year mark, respectively. This indicated a higher cumulative CIN 3+ incidence rate in our subjects at the one-year

mark than was found in Egemen's work at 1.6 percent [9]. The same can be said in this study's comparison to Ciavattini (0.7 percent) [10]. These results are detailed in Table 3.

**Table 3.** Comparison of remission and progression rate of CIN 1 in various studies.

| Study | Present study | Egemen D | Loopik DL | Ciavattini A | Nogara P | Zheng B |
|---|---|---|---|---|---|---|
| Year | 2020 | 2020 | 2019 | 2017 | 2013 | 2017 |
| Country | Thailand | California | Netherlands | Italy | Brazil | China |
| Age (year) | 25 - 65 | 25 - 65 | 21 - 24 | 36.9 ± 9** | 16 – 61 | 38.4** |
| Test | Co | Co | Cyt | Cyt, Co | Cyt | Cyt, Co |
| HPV | mRNA | HC-2 | NA | NA | NA | HC-2 |
| CIN1 f/u (y) | 3 | 1-5 | 1 | 2 | 1 | 0.5 |
| Remission* | 87.5 | NA | 62.0 | 88.5 | 89.4 | 14.9 |
| CIN3+ rate | | | | | | |
| 1 year* | 2.24 | 1.6 | 6.4 | NA | 9.4 | NA |
| 2 year* | 4.53 | NA | NA | 0.7 | NA | NA |

*%, **mean ± SD (standard deviation), CIN: cervical intraepithelial neoplasia, Co: Co-testing, Cyt: Cytology, HPV: Human papillomavirus, mRNA: detection of HPV infection by using messenger RNA technology, HC-2: detection of HPV DNA using Hybrid Capture 2 technology, NA: not available, (y): year of follow up during the study, f/u: follow - up, Remission: Remission rate of CIN 1, CIN 3+ rate: cumulative incidence rate of CIN 3+

At the one-year follow-up, in LSIL cases with either negative or positive HPV results, most Thai physicians performed colposcopies as also seen in cases of ASC-US with positive HPV results. However, in cases of ASC-US with negative HPV results, some Thai physicians decided on colposcopy instead of cytology or HPV testing for follow-up as well. The diagnostic power of colposcopy yielded a definitive diagnosis with more certainty than the screening method. In Thailand, the cost of colposcopy is covered by Thai Universal Health Coverage while its costs are much higher than the screening method in developed countries. ASCCP 2019 guidelines recommend screening follow-ups at one or three years in lieu of colposcopy. In this regard, Thai practices have advantages in Thailand when compared to the USA (from where ASCCP guidelines originate) due to the prevalence of socialized healthcare programs.

While reviewing standard cervical cancer screening guidelines such as the ASCCP 2019, American Cancer Society (ACS), and World Health Organization (WHO), some discrepancies were identified in the conventional testing, liquid-based, visual inspection of the cervix with acetic acid (VIA), co-testing and primary HPV screening. The aforementioned guidelines also had differences with regard to population characteristics. Cumulative incidence risks of CIN 3 and cervical cancer were described as lower when compared to the Thai population according to epidemiological studies [8, 14, 15]. Globocan, in 2020, reported that the age-standardized incidence rates of cervical cancer (ASR) in Northern America, Central America, and worldwide were 6.1, 13.8, and 13.3, respectively. Within the same study, the ASR for South-Eastern Asian countries was 17.8 [3]. This was a significantly higher result when compared to the rest of the world, especially in North America. Thus, the follow-up intervals (3-5 years) detailed in the current ASCCP recommendations may not appropriately account for the varying incidence rates across different regions of the world, as the current recommendations are modeled on data from North America.

Despite the clear discrepancy in population and cumulative incidence risk, the national policy in Thailand still recommends follow-up intervals similar to that recommended by ASCCP guidelines [6].

With the information at hand, in conjunction with the results from this study, we recommend shorter follow-up intervals in CIN 1 histology since the cumulative incidence rate of CIN 3 among CIN 1 cases was higher in this study population, which is more specifically representative of the local Thai population.

The current Thai National Health Security Office (NHSO) policy for HPV vaccine administration in patients aged 9-13 years with a complete two doses has only recently begun. However, a shortage of vaccines caused the Thai government to be unable to reach its vaccination target. So, millions in Thailand remain unvaccinated for HPV [16]. However, the effects of this policy cannot be evaluated for some ten years, which prompts the need for more immediate data to be collected. In contrast, HPV vaccination programs in the United States and Australia featured a more comprehensive vaccine coverage that had been implemented for longer periods and thus yielded more long-term data and results with vaccines in the United States being offered to both male and female populations [17, 18]. Thus, ASCCP 2019 guidelines are more applicable in these populations with more comprehensive vaccine coverage than Thailand.

To further illustrate this point, the HPV vaccine coverage in this study only encompassed 20 percent of the population enrolled. Even with this low number, most of the participants were also administered post-exposure HPV vaccine prophylaxis rather than pre-exposure HPV vaccine prophylaxis. The quality of vaccine coverage identified may indicate that the percentage of patients with proper HPV vaccine administration in Thailand may be lower than the percentage of patients with proper HPV vaccine coverage who were enrolled in the ASCCP guideline study [8].

In this study, patients were not followed up with at five years, as is detailed in ASCCP guidelines. Participants were followed up with for shorter intervals or were administered treatment or received diagnoses before the five-year follow-up recommendation. As a result, the findings from this study might not be as comprehensive as the current ASCCP guidelines [8].

## 4. Conclusion

Follow-up care for Thai patients with CIN 1 should be more aggressive and more frequent than ASCCP guidelines due to the higher local incidence of CIN 3, cervical cancer incidence rates, and differences in cohorts receiving HPV vaccine administration.

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