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Original Article

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Risks of cervical intraepithelial neoplasia grade 3 or invasive cancers in ASCUS women with different management: a population-based cohort study

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ABSTRACT

Objective: To investigate the progression risk of atypical squamous cells of undetermined significance (ASCUS) with different clinical managements.
Methods: Women with their first diagnosis of ASCUS cytology were retrieved from the national cervical cancer screening database and linked to the national health insurance research database to identify the management of these women. The incidences of developing cervical intraepithelial neoplasia grade 3 and invasive cervical cancer (CIN3+) were calculated, and the hazard ratios (HRs) were estimated using a Cox proportional hazards model. This study was approved by the Research Ethics Committee of the National Taiwan University Hospital and is registered at ClinicalTrials.gov (Identifier: NCT02063152).
Results: There were total 69,741 women included. Various management strategies including colposcopy, cervical biopsies and/or endocervical curettage, and cryotherapy, failed to reduce the risk of subsequent CIN3+ compared with repeat cervical smears. Loop electrosurgical excision procedure/conization significantly decreased risk of subsequent CIN3+ lesions (HR=0.22; 95% confidence interval [CI]=0.07–0.68; p=0.010). Women in their 40s–50s had an approximately 30% risk reduction compared to other age groups. Women with a previous screening history >5 years from the present ASCUS diagnosis were at increased risk for CIN3+ (HR=1.24; 95% CI=1.03–1.49; p=0.020).
Conclusion: In women of first-time ASCUS cytology, a program of repeat cytology can be an acceptable clinical option in low-resource settings. Caution should be taken especially in women with remote cervical screening history more than 5 years.

Keywords: Atypical Squamous Cells of Undetermined Significance; Cervical Intraepithelial Neoplasia Grade III; Uterine Cervical Neoplasms; Colposcopy; Cervical Biopsy; Cryotherapy

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: C.C.A., C.W.F.; Data curation: H.H.C., C.Y.Y.; Formal analysis: H.H.C., C.Y.Y.; Funding acquisition: C.C.A.; Methodology: C.C.J., Y.S.L.; Project administration: C.C.J.,Y.S.L.; Supervision: C.C.A.; Writing - original draft: T.Y.J.; Writing - review & editing: T.Y.J., C.W.F., C.C.A.

INTRODUCTION

Cervical cytology is the standard of care for cervical cancer screening [1-3]. In Taiwan, a substantial reduction in the incidence of cervical cancer occurred after the implementation of the screening program in 1995 [4]. The age-adjusted incidence was from 57.8/100,000 person-years in 1996 to 26.2 in 2006 with a 54.7% reduction [1]. Between 4% and 5% of Pap smears performed yearly are interpreted as atypical squamous cells (ASCs) of undetermined significance (ASCUS) [5]. Since 1988 the Bethesda System has used a new nomenclature for ASCs to report cytology findings on Pap smears and ASC represents a poorly defined diagnosis. The 2001 Bethesda System then subdivided the ASC category into ASCUS and ASC, which cannot exclude high-grade squamous intraepithelial lesions [6].

ASCUS represents an undefined entity because atrophy, benign inflammation, reactive changes to a transient human papillomavirus (HPV) infection, and preparation artifacts can mimic intraepithelial lesions; however, ASCUS cytology is rarely associated with significant pathology [7,8]. Management of ASCUS cytology was a matter of debate. It was until the association between HPV infection and cervical neoplasia to be established, which led to a triage study involving ASCUS and low-grade squamous intraepithelial lesion (LSIL) cytology (the ASCUS-LSIL Triage Study [ALTS]) with HPV assays [9,10]. The 2-year cumulative risk of cervical intraepithelial neoplasia grade 3 and invasive cervical cancer (CIN3+) within the ASCUS population was reported to be 8%–9% based on a single ASCUS interpretation in the ALTS [10]. HPV triage detected 72.3% of cumulative cases of cervical intraepithelial neoplasia (CIN) 3 with significant greater sensitivity than immediate colposcopy or conservative management (sensitivity for CIN3, 53.6% and 54.6%, respectively). ALTS evaluated these 3 alternative strategies in a prospective, randomized fashion and concluded HPV triage was a most effective strategy for management of women with ASCUS. ALTS did not formally evaluate other potential methods such as direct visual inspection with acetic acid for ASCUS triage and there were insufficient data to justify the clinical use of these tests. Therefore, it is critical to find a cost-effective clinical strategy to identify patients within the ASCUS population who will develop CIN3+ lesions and treat them optimally. A recent study involving 13,734 screenees for ASCUS/LSIL in Netherlands using repeat cytology at 6 months, or with additional high-risk HPV (hrHPV) testing at 6 months showing additional hrHPV testing, was to shorten the follow-up interval without altering the detection of CIN3+ [11].

When considering risk estimation for pre-cancer and cancer in women with ASCUS cytology, but without available HPV testing and whether or not to “treat,” there was no study to provide the optimal management or treatment for reducing the risk of ASCUS cytology to develop pre-cancerous and invasive cancerous lesions. Cervical cancer screening program in Taiwan has been established since 1995. Therefore, we designed a cohort study to assess the screening status, clinical characteristics, and the managements of women with first-time ASCUS cytology and the risks of developing CIN3+ lesions. The purpose of our study was to evaluate which management or procedure might alter the clinical outcome of women with cytologic ASCUS.

MATERIALS AND METHODS

In 1995, the annual cervical screening program using the Pap test was launched in Taiwan for women 30 years and older. Women diagnosed with ASCUS during the period from January 1, 2004 to December 31, 2007, were retrieved from the database of the Taiwan Cervical Cancer

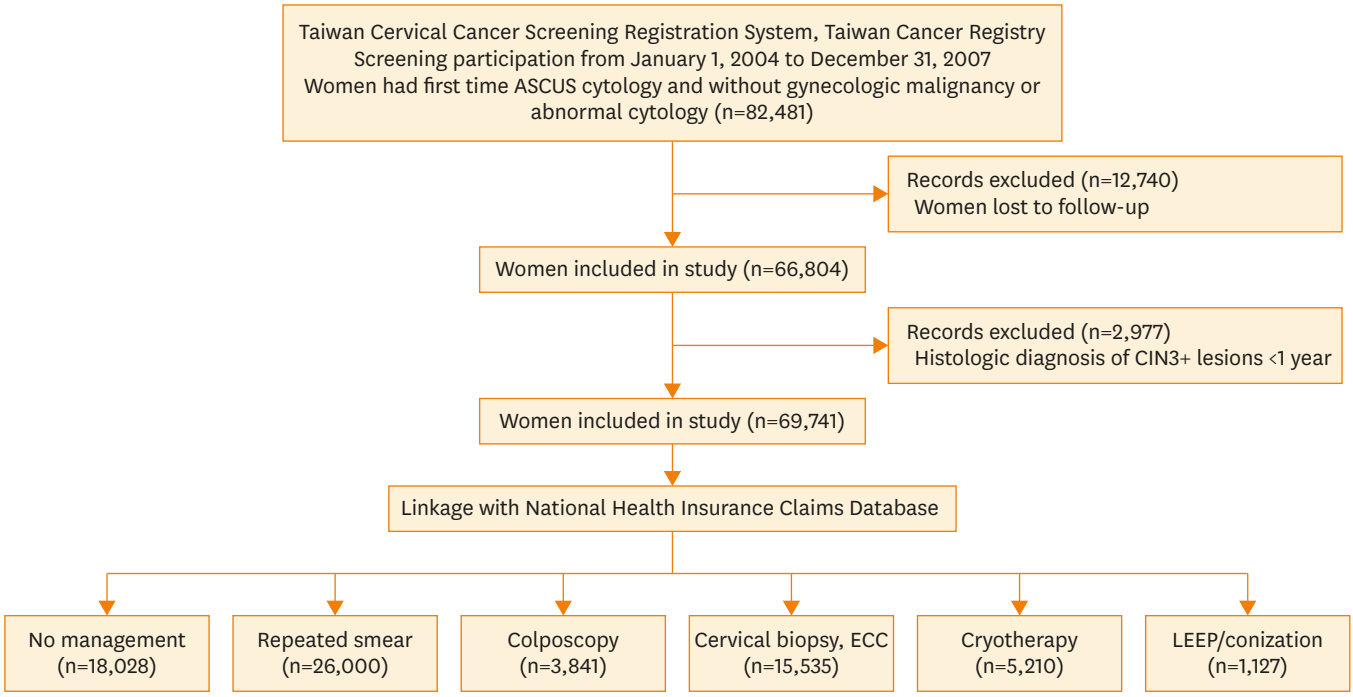

Fig. 1. Flow of the study population among all women who attended cervical cancer screening with ASCUS cytology during 2004–2007.
ASCUS, atypical squamous cells of undetermined significance; CIN3+, cervical intraepithelial neoplasia grade 3 and invasive cervical cancer; ECC, endocervical curettage; LEEP, loop electrosurgical excision procedure.

Screening Registration System. Registered data included personal identification information, date of birth, date of diagnosis, histological diagnosis, and treatment (**Fig. 1**). To identify eligible women, databases from the Taiwan Cervical Cancer Screening Registry, Taiwan Cancer Registry, and National Health Insurance Claims Database were used to retrieve information.

Women with a history of (pre)malignant cervical lesions, abnormal cervical smears or any surgery in the area of the cervix were excluded. Besides, women with an underlying gynecologic malignancy (malignancies involving the uterine corpus, cervix, ovary, and vagina, and trophoblastic neoplasia), an abnormal Pap smear (including CIN, atypical cells, or malignant cells) before the detection of ASCUS, and a history of a trachelectomy or hysterectomy were also excluded in this. If the interval between Pap test (ASCUS) and the diagnosis of CIN3+ lesion including CIN3 lesion, adenocarcinoma in situ (AIS) and invasive cervical cancer was less than one year, it was regarded as an undetermined CIN3 lesion, AIS or invasive cervical cancer, and was also excluded for analysis.

We investigated what management done "within one year" of ASCUS cytology would reduce the risk of CIN3+ 1 year after. Screening intervals were categorized to facilitate analysis. The official Pap screening with interval of one year is advocated in Taiwan with annual reimbursement in contrast to the interval of 3 years in most countries. After the screening program launched in Taiwan, the triennial and 5-year participation rate was 51.0% and 63.5% in 2007 [4] despite the triennial screening rate approached 70% in 2016. Therefore, we categorized screening intervals into 4 groups as <1, 1–3, 3–5, >5 or never. To obtain clinical management information, women with ASCUS cytology were computer-linked to the National Health Insurance Claims Database using their unique national identification numbers and the clinical management information was retrieved, including various follow-up procedures such as repeated Pap smear,

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colposcopy, cervical biopsy and/or endocervical curettage (ECC), excisional procedure (loop electrosurgical excision procedure [LEEP] or conization), and cryotherapy of the cervix. All of the follow-up procedures performed within 1 year after the detection of ASCUS cytology were then recorded irrespective the procedures thereafter. Those who did not receive any of the above-mentioned procedures were defined as "no management group." If women with ASCUS cytology underwent more than one procedure, thus the most aggressive procedure for clinical management classification was chosen. For example, if a colposcopy, and cervical biopsy and/or ECC were both performed, the patient was counted into the cervical biopsy/ECC group. If a cervical biopsy and LEEP/conization were both performed, the patient was counted into the LEEP/conization group. Follow-up procedures were judged by clinicians to determine which patients fall into a no management group versus repeat smears, colposcopy, biopsy, or LEEP.

The follow-up period was defined as since 1 year after ASCUS cytology to the time CIN3+ lesion diagnosed, the date of death, or December 31, 2010, whichever date came first. CIN3+ lesions included CIN3, AIS, and invasive cervical cancer. CIN3+ lesions were coded based on the International Classification of Diseases for Oncology (third revision; T-code C53) in the Taiwan Cancer Registry database, which is considered to be complete with the percentage of cervical cancers identified by death certificates at <1% of all incident cervical cancer cases and accurate with cervical cancer morphologic verification >99% during the study period [12]. The death certificate registry, which is also considered to be accurate with a high concordance of cervical cancer deaths between reviewers and original coders (κ=0.94) [13], was linked to obtain the date of death. For evaluating the impact of clinical management in women with ASCUS cytology, incidence and hazard ratios (HRs) were estimated. The incidence of CIN3+ lesions in women of different clinical management strategies was calculated by dividing the number of CIN3+ cases by the person-years at risk of developing CIN3+ lesions. The HRs and 95% confidence intervals (CIs) adjusted for age, educational status, residency, and previous screening compliance were estimated using Cox regression. Statistical significance levels were determined using a 2-tailed test and a p-value <0.05 was considered statistically significant. Statistical analysis was performed using SAS software (version 9.3; SAS, Inc., Cary, NC, USA).

1. Ethics approval and consent to participate

The research protocol was approved by the Ethical Committee of the Bureau of the Health Promotion, Department of Health, Taiwan. This study was approved by the Research Ethics Committee of the National Taiwan University Hospital and is registered at www.ClinicalTrials.gov (Identifier: NCT02063152). The computerized linkage of all national profiles was conducted by the Taiwan Cervical Cancer Prevention Surveillance Center according to standardized protocols. Permission to use the national profiles in this study was obtained from the Health Promotion Administration and The Collaboration Center of Health Information Application in the Ministry of Health and Welfare in Taiwan.

RESULTS

Between January 1, 2004 and December 31, 2007, of 82,481 women with a first diagnosis of ASCUS cytology were identified. The 12,740 women lost to follow-up were excluded. The 2,977 women who had CIN3+ lesion diagnosed within one year were also excluded due to the occult CIN3+ lesion. And finally a total of 69,741 women were included in the current study for further analysis. There were 266,011 person-years of follow-up, with an average follow-up period of 3.81 years for each woman. During this period, a total of 772 cases of CIN3+ lesion

were identified and the overall incidence was 290.2 per 100,000 person-years. The incidences of these 69,741 women and their subsequent CIN3+ lesion by age distribution, screening history, educational status, and management are shown in **Table 1**.

The risks of developing CIN3+ lesion in women with ASCUS cytology are shown in **Table 2**. The women in 40–49 (HR=0.73; 95% CI=0.60–0.88; p<0.001) and 50–59 (HR=0.61; 95% CI=0.48–0.78; p<0.001) year-old groups had significantly lower risk of subsequent CIN3+ lesions compared with those in 30–39-year-old group (HR regarded as 1.00). Women whose last previous screening interval less than 1 year (HR=0.77; 95% CI=0.62–0.94; p=0.010) also had significantly lower risk of subsequent CIN3+ lesions as compared with those whose last previous screening interval were 1 to 3 years. Whereas, women who had last previous screening interval longer than 5 years or never received screening had significantly higher risk of subsequent CIN3+ lesion (HR=1.24; 95% CI=1.03–1.49; p=0.020).

The influence of management of women with ASCUS cytology is shown in **Table 2**. When regarding the incidence of CIN3+ lesion in women who had repeated Pap smears as the compared baseline (HR as 1.00), women in "no management" group were at increased risk for subsequent CIN3+ lesions (HR=1.39; 95% CI=1.17–1.66; p<0.001). Women who had colposcopy alone, cervical biopsy and/or ECC, or cryotherapy did not increase or decrease the risk of CIN3+ lesions. Women had LEEP/conization significantly decreased risk of subsequent CIN3+ lesions (HR=0.22; 95% CI=0.07–0.68; p=0.010).

Table 1. Baseline characteristics of 69,741 women with ASCUS cytology according to age distribution, screening interval, educational status, management, and incidence of subsequent CIN3+

Characteristics	No. of ASCUS patients	Person-years of follow-up	No. of CIN3	No. of invasive cancer	No. of CIN3+	Incidence of CIN3+ per 100,000 person-years*
Total	69,741	266,011	669	103	772	290.2
Age (yr)						
20–29	6,136	24,263	71	3	74	305.0
30–39	19,193	73,320	227	29	256	349.2
40–49	22,448	85,621	179	42	221	258.1
50–59	13,999	52,798	100	19	119	225.4
60–69	5,423	20,580	68	5	73	354.7
>70	2,542	9,429	24	5	29	307.6
Previous screening interval (yr)						
<1	15,368	60,333	105	22	127	210.5
1–3	31,505	118,413	307	23	330	278.7
3–5	7,927	29,703	84	23	107	360.2
>5 or never	14,941	57,562	173	35	208	361.3
Educational status						
<6 years of schooling	15,210	58,696	146	28	174	296.4
Junior high school	11,923	45,686	115	19	134	293.3
Senior high school	24,541	93,593	242	45	287	306.6
College or graduate school	17,412	65,567	165	11	176	268.4
Management						
No management	18,028	68,557	198	59	257	374.9
Non-interventional procedures						
Repeated Pap smear	26,000	99,659	232	27	259	259.9
Colposcopy	3,841	14,208	28	4	32	225.2
Cervical biopsy and/or ECC	15,535	58,765	172	6	178	302.9
Interventional procedures						
Cryotherapy	5,210	20,267	36	7	43	212.2
LEEP/conization	1,127	4,555	3	0	3	65.9

Data are number (%) unless otherwise specified.
ASCUS, atypical squamous cells of undetermined significance; CIN3, cervical intraepithelial neoplasia grade 3; CIN3+, cervical intraepithelial neoplasia grade 3 and invasive cervical cancer; ECC, endocervical curettage; LEEP, loop electrosurgical excision procedure.
*Age-adjusted incidence rate of CIN3+ per 100,000 person-years.

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Table 2. Multivariate analysis of the risk of subsequent CIN3+ lesion in 69,741 women with ASCUS cytology

Variables	HR	95% CI of HR	p
Age (yr)			
20–29	0.77	0.59–1.00	0.060
30–39	1.00		
40–49	0.73	0.60–0.88	<0.001
50–59	0.61	0.48–0.78	<0.001
60–69	0.90	0.66–1.23	0.500
>70	0.72	0.47–1.11	0.140
Previous screening interval (yr)			
<1	0.77	0.62–0.94	0.010
1–3	1.00		
3–5	1.25	1.00–1.55	0.050
>5 or never	1.24	1.03–1.49	0.020
Educational status			
<6 years of schooling	1.00		
Junior high school	0.98	0.76–1.26	0.860
Senior high school	0.96	0.75–1.22	0.720
College or graduate school	0.80	0.61–1.04	0.100
Management			
No management	1.39	1.17–1.66	<0.001
Non-interventional procedures			
Repeated Pap smear	1.00		
Colposcopy	0.80	0.55–1.16	0.240
Cervical biopsy and/or ECC	1.05	0.87–1.28	0.590
Interventional procedures			
Cryotherapy	0.76	0.55–1.05	0.100
LEEP/conization	0.22	0.07–0.68	0.010

ASCUS, atypical squamous cells of undetermined significance; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 and invasive cervical cancer; ECC, endocervical curettage; HR, hazard ratio; LEEP, loop electrosurgical excision procedure.

The cumulative risks of subsequent CIN3+ lesions in women of ASCUS cytology with various management modalities showed a significant difference (p<0.001, log-rank test; **Fig. 2**).

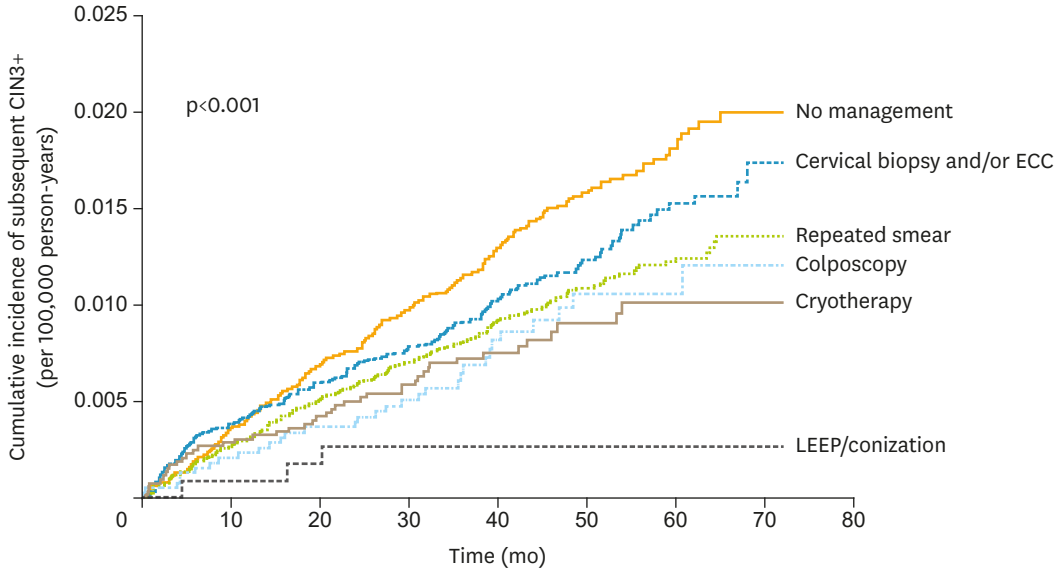

Fig. 2. Survival analysis of subsequent risk for CIN3+ diagnosis in 69,741 women with ASCUS cytology according to management. X-axis refers to follow-up time in months since 1 year after the ASCUS cytology. Y-axis refers to cumulative incidence of subsequent CIN3+.
ASCUS, atypical squamous cells of undetermined significance; CIN3+, cervical intraepithelial neoplasia grade 3 and invasive cervical cancer; ECC, endocervical curettage; LEEP, loop electrosurgical excision procedure.

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DISCUSSION

In our study all treatments, except LEEP/conization, done within one year of ASCUS cytology were not protective from subsequent CIN3+ compared to repeated smears. Women without any management after ASCUS cytology were significantly of increased CIN3+ risk. Middle-aged women (40–59 years of age) were at decreased risk for CIN3+ compared to women 30–39 years of age. Women with a screening interval >5 years before ASCUS detection were at higher risk for subsequent CIN3+.

ALTS [10] reported options including immediate colposcopy, accelerated repeat Pap and hrHPV test for managing ASCUS are safe and effective. Colposcopy is suggested for women with ASCUS or greater cytologic abnormalities in the repeat tests; or HPV tests is taken and women who were hrHPV DNA negative can be followed-up with repeat cytology at 12 months while those who with positive test should be referred for colposcopic evaluation; or, immediate colposcopy in all women with ASCUS is an alternative option. Reflex HPV testing was advised in the 2012 American Society for Colposcopy and Cervical Pathology (ASCCP) consensus guidelines for management of women with ASCUS. Compared with colposcopy for all ASCUS, reflex testing followed by colposcopy for HPV-positive women identified most CIN3 lesions yet referred fewer women to colposcopy. The practice guideline on management of ASCUS in Taiwan includes colposcopic exam, follow-up cytology in 3–6 months interval, or HPV triage.

HPV triage substantially increased colposcopy referrals compared with serial cytology despite its higher sensitivity. Our previous cohort study revealed that older women (older than 60 years) were at higher risk for developing invasive cervical cancer compared with younger women in the unscreened group with a first diagnosis of ASCUS [14], and also reflected that transient infections with HPV and associated cytologic and histologic changes were common in younger women. The reported prevalence of hrHPV among women with ASCUS in most studies is 33%–51% [15] and the rate is highly age-related, which is as high as 70% for women <25 years of age [16]. A history of prior screening is also crucial for risk assessment due to the higher risk in the unscreened group, thus HPV DNA testing is recommended.

Spontaneous regression in the majority of women with minor cytologic cervical abnormalities has been reported, which is a manifestation of transient HPV infection, hence management with observation is advocated [17]. The risk of invasive cervical cancer in women with ASCUS is low because one-third to two-thirds of ASCUS smears are not associated with hrHPV infections [10,18]. Spontaneous regression is anticipated and this is likely why procedures, such as biopsies and cryosurgery, showed no benefits in risk reduction of future CIN3+ in our study. Immediate colposcopy has been considered to be an option for ASCUS cytology, but colposcopy is experience-dependent and sometimes leads to overtreatment of lesions that would regress from a transient HPV infection. The prevalence of CIN2+ among women with ASCUS is between 5% and 12% [10] hence the positive predictive values of immediate colposcopy to detect all CIN2, CIN3, and invasive lesions are low.

No risk reduction was observed with colposcopy and cervical biopsy as compared with serial cytology in the current study because women with a CIN3+ diagnosis within one year of enrollment of ASCUS cytology were excluded, assuming the diagnosis reflected an occult disease and not a disease course per se. Cryotherapy may enhance regression of CIN lesions through the destruction of atypical cells caused by HPV infections, or induction of

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local inflammatory responses, and thereby cell-mediated immune responses. In a meta-analysis performed by Sauvaget et al. [19], cryotherapy achieved a cure rate of 94% in CIN1, 92% in CIN2, and 85% in CIN3, with an increased cure rate in the absence of endocervical involvement; however, no prior study has reported and supported this protective effect of cryotherapy on minor cytologic atypia. Cryotherapy failed to increase the clearance of prevalent HPV infections among women with LSIL with a clearance rate at 1 year of 89.7% in the cryotherapy group and 90.3% in the observation group [20]. In the current study, women with ASCUS cytology who underwent cryotherapy did not have risk reduction for subsequent CIN3+; the effect of cryotherapy on HPV clearance in the ASCUS population has yet to be studied. LEEP/conization was associated with a significantly lower risk of subsequent CIN3+ (HR=0.22; 95% CI=0.07–0.68; p=0.010). This risk reduction was possibly related to more tissue damage caused by LEEP/conization as compared to cryotherapy which induced a stronger immune response against HPV infection even though the effect of LEEP/conization in ASCUS management is not based on strong evidence. Immediate LEEP/conization probably excised a lesion rather simply diagnosed is and reflected gross overtreatment.

ECC was optional with potential selection bias and routine performance of ECC in those women is controversial. Poomtavorn et al. [21] reviewed 260 patients with ASCUS and LSIL cytology who underwent an ECC at the time of colposcopic examination and the frequency of high-grade endocervical dysplasia was low (CIN2–3 in 3.1%). We correlated the pathology reports from the cervical biopsy registry within one year after ASCUS cytology which showed no significant risk reduction of subsequent CIN3+ in those reporting CIN1 (data not shown) whether or not further intervention such as cryotherapy or LEEP/conization was given. For women with biopsy-proven CIN1, conservative management is justified and not hazardous. Despite the small decrease in risk of subsequent CIN3+, LEEP or conization raised the risk of preterm delivery [22,23], while ablation of the transformation zone by cryotherapy or electrocauterization sometimes results in cervicitis, scarring, cervical stenosis, and even inadvertent ablation of invasive cervical cancer. Multiple treatment modalities reflect the heterogenicity of ASCUS cytology, which allows conservative management, especially for young women for whom future fertility is an issue of concern for LEEP/conization was not devoid of short term and longer term adverse effects.

Our study also showed protective age factors with a bimodal distribution for adolescent (20–29 years; HR=0.77; 95% CI=0.59–1.0; p=0.060) and peri-menopausal age (40–49 and 50–59 years) associated with reduced risk (HR=0.73; 95% CI=0.60–0.88; p<0.001 and HR=0.61; 95% CI=0.48–0.78; p<0.001, respectively). These findings are compatible with the age-specific HPV distribution with the first peak of HPV infection detected after the onset of sexual relations and a second peak in older women [24]. The first peak reflects transient infection that clears spontaneously and the second peak is postulated to be associated with immunosenescence, a change in sexual behavior during middle age, a cohort effect of HPV persistence, and the hormonal effect on cytology in the peri-menopause. In the study of genotypes in 784 Taiwanese women with abnormal Pap smear (ASCUS or greater) [25], the proportion of patients with HSILs who were older than 40 years and infected with hrHPV other than HPV 16/18 (76.6%) was significantly higher than those with HPV 16/18 (20.3%) (p<0.001). Hammer et al. [26] also reported the percentage positive for HPV 16 or 18 decreased from 78.1% in women aged 55–60 years to 45.4% in women ≥75 years (p<0.001) in 153 cases of cervical cancer. A decreased HPV 16/18 in peri-menopausal women probably explained why a lower risk of CIN3+ in our study. A HPV DNA test for ASCUS triage is not included in the national screening program in Taiwan, thus rendering it difficult to evaluate

the role of HPV DNA testing in women with cytologic ASCUS. However, in the study of HPV genotypes in women with ASCUS conducted by Chiang et al. [25], hrHPV comprised 51% and HPV positive rate was 38.3% for women with ASCUS/AGUS cytology from the Taiwan Cooperative Oncologic Group study [27]. These results were consistent with HPV prevalence reported in other countries.

Current guidelines for the management of ASCUS include HPV testing and repeat cytology smears at specific intervals [28-30]. The limitation of our study was the lack of HPV DNA data for women with cytologic ASCUS and the study was not a randomized controlled one. A total of 12,740 women lost to follow-up in this study thus data were not included in our analysis which might lead to potential bias. A separate analysis (data not shown) on these women showed they were significant older, screened less often and had lower educational performance compared to the women in present study. Managements were judged by clinicians subjectively without following similar standards or guidelines therefore management strategy was based on individual's risk and the results should be interpreted cautiously. Despite the limitations, the sample size in our population-based cohort study was sufficient and evidence-based management guidelines for ASCUS cervical cytology is well-established according to National Health Research Institutes of Taiwan. Our study was based on the National Health Insurance Claims database, which has a high coverage rate of cervical cytology screening due to reimbursement by the National Health Insurance. Without introducing HPV assays, no prior study has directly compared the treatment effect of different modalities (including follow-up cytology, immediate colposcopy, cervical biopsy, cryotherapy, or LEEP/conization) among the ASCUS population, nor were the relative and cumulative risks of subsequent CIN3+ for each management strategy determined. The results may be useful in the regions without available HPV testing or where HPV testing not included in primary screening making its practical values outweigh the limitations.

The incidences of developing CIN3+ lesions in the women with cytologic ASCUS were different among various age groups. The incidences of CIN3+ lesions were higher in women younger than 30 years old and those older than 60 years old in this survey (**Table 1**). Women younger than 30 years are outside the usual screening age in the cervical cancer screening program in Taiwan at present. Women older than 60 years old can be expected that they may seldom visit the clinicians for regular follow-up after diagnosed ASCUS. They may visit the clinicians when displaying other gynecologic symptoms.

In summary, our study offers evidence that serial smears are safe in women with a first diagnosis of ASCUS cytology and highlights expectant management for resolution of HPV infection instead of overtreatment. Among various management strategies done within one year after first-time ASCUS cytology, colposcopy, cervical biopsy or cryotherapy did not decrease the risk of subsequent CIN3+ lesions. A program of repeat cytology can be an acceptable clinical option in low-resource settings. Caution should be taken especially in women >60 years of age or with remote cervical screening history more than 5 years.

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