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Prognostic value of human papillomavirus 16/18 genotyping in low-grade cervical lesions preceded by mildly abnormal cytology*

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Abstract: Histological low-grade squamous intraepithelial lesion/cervical intraepithelial neoplasia grade 1 (LSIL/CIN1) preceded by normal or mildly abnormal cytology is recommended for conservative follow-up, with no separated management. In this study, we assessed the triage value of human papillomavirus (HPV) 16/18 genotyping in 273 patients with LSIL/CIN1. HPV16/18 genotyping was performed at baseline and follow-up was at 6-monthly intervals for up to 2 years. At each follow-up, women positive for cytology or high-risk HPV (hrHPV) were referred for colposcopy. Enrollment cytology, HPV16/18 genotyping, and questionnaire-obtained factors were linked to the 2-year cumulative progression rate. Univariate and multivariate analyses were performed taking into account time-to-event with Cox proportional hazard regression. The results showed that 190 cases (69.6%) regressed, 37 (13.6%) persisted, and 46 (16.8%) progressed. HPV16/18 positivity (hazard ratio (HR), 2.708; 95% confidence interval (CI), 1.432–5.121; P=0.002) is significantly associated with higher 2-year cumulative progression rate. Sub-analysis by enrollment cytology and age restricted the positive association among patients preceded by mildly abnormal cytology and aged 30 years or older. Immediate treatment is a rational recommendation for the high-risk subgroup, when good compliance is not assured.

Key words: Low-grade squamous intraepithelial lesion (LSIL); Cervical intraepithelial neoplasia grade 1 (CIN1); Human papillomavirus (HPV); HPV16/18 genotyping; Prognostic value; Prospective study

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1 Introduction

Histological low-grade squamous intraepithelial lesion (LSIL), also termed cervical intraepithelial neoplasia grade 1 (CIN1) in the prior edition of three-tier terminology, is limited to the basal one-third of the squamous epithelium. Up to 70%–80% of LSIL/CIN1 will regress spontaneously, while a subset is associated with residual risk for future precancerous lesion (Schiffman *et al.*, 2007; Martin and O'Leary, 2011). No reliable biomarker, other than cytology, has been used to predict the evolution of LSIL/CIN1. Kaiser Permanente Northern California (KPNC) data showed a relatively low 5-year progression rate of LSIL/CIN1 preceded by normal cytology (negative for intraepithelial lesion or malignancy (NILM)) or mildly abnormal cytology (atypical squamous cells of undetermined significance (ASC-US) and LSIL), but a substantially higher progressive risk with more severe abnormalities (high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells—cannot rule out HSIL (ASC-H), and atypical glandular cells (AGC)) (Katki *et al.*, 2013). Accordingly,

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LSIL/CIN1 preceded by normal or mildly abnormal cytology is considered low-risk and recommended for conservative follow-up only (Massad *et al.*, 2013), with no triage management available. Yet up to 10% of progression was reported for these patients (Katki *et al.*, 2013). Previous studies have explored the values of immunohistochemical markers (such as $p16^{INK4A}$ and cytokeratin 7) in predicting the behavior of LSIL/CIN1. However, microscopically interpretive variability confounded such studies, and results have been inconsistent (Liao *et al.*, 2014; Mills *et al.*, 2015; Huang *et al.*, 2016; Paquette *et al.*, 2016; Sagasta *et al.*, 2016).

Human papillomavirus (HPV) genotypes have different carcinogenicities, leading us to wonder whether HPV genotyping could be of clinical value in refining the management of LSIL/CIN1. HPV16/18 genotyping is the most approved genotyping strategy. Progressive risk is elevated for women with positive HPV16/18, even when cytology is normal (Khan *et al.*, 2005). Thus, HPV16/18 positivity alone is an indication for colposcopy referral among women aged 30 years or older, according to the current American Society for Colposcopy and Cervical Pathology (ASCCP) management guidelines (Massad *et al.*, 2013). Yet no prospective study has addressed the prognostic value of HPV16/18 genotyping in LSIL/CIN1 preceded by non-severe cytology abnormalities. We conducted this hospital-based longitudinal study to evaluate the performance of HPV16/18 genotyping as a triage for LSIL/CIN1 preceded by normal or mildly abnormal cytology.

2 Materials and methods

2.1 Patient recruitment

Women with LSIL/CIN1 diagnosed by colposcopy-guided biopsy (colposcopy is adequate and endocervical curettage is negative) were prospectively recruited in the Women's Hospital, School of Medicine, Zhejiang University, China during June 2012 to December 2013. The diagnostic criterion was intraepithelial lesion limited to the basal one-third of the squamous epithelium, exclusive of flat condyloma, koilocytotic atypia, and koilocytosis. Women were excluded from this study according to the following criteria: (1) preceded by cytological HSIL, ASC-H, or AGC; (2) surgically or ablatively treated cervix; (3) previously confirmed cervical cancer or precursor, or other malignancies; (4) with immunosuppressive diseases; and, (5) pregnancy. All eligible patients underwent HPV16/18 genotyping at baseline. Information on socio-demographic characteristics, reproductive history, contraception, menstrual status, and sexual behavior was collected via an interviewer-administered structured questionnaire.

2.2 Ethics approval and consent to participate

This study was approved by the Human Research Ethical Committee of the Women's Hospital, School of Medicine, Zhejiang University, China with protocol No. 20110014. Informed consent was obtained from study participants according to institutional guidelines.

2.3 Follow-up

Patients were followed up at 6-monthly intervals for up to 2 years. At each follow-up, liquid-based cytology and HPV genotyping were performed as first-level exams. Women with positive cytology or high-risk HPV (hrHPV) were referred for colposcopy. The endpoints were defined as follows: (1) progression: histology-confirmed HSIL or more; (2) regression: cytology normal and hrHPV negative, or cytology/hrHPV positive but histology negative; and, (3) persistence: histology-confirmed LSIL/CIN1. Women reaching an endpoint would then be handled according to the ASCCP management guidelines (Massad *et al.*, 2013).

2.4 Cytology and HPV genotyping

Hospital cytologists performed cytological diagnosis according to the 2001 Bethesda System (Solomon *et al.*, 2002). HPV genotyping was carried out with HPV GenoArray test kit (Hybribio, Hong Kong, China), which was described in our previous studies (Ye *et al.*, 2010a; 2010b). Briefly, this test kit can identify 14 hrHPVs (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) separately.

2.5 Colposcopy and histological diagnosis

Hospital colposcopists performed colposcopy according to the standardized protocol and hospital pathologists made histological diagnoses according to the Lower Anogenital Squamous Terminology (LAST)

recommendations (Darragh *et al.*, 2012). Consensus on histodiagnosis was reached by an expert panel in the event of disagreement.

2.6 Statistical analysis

Enrollment cytology, HPV16/18 genotyping, and potential risk factors identified from the questionnaire were assessed as independent prognostic markers for 2-year cumulative progression. In both univariate and multivariate analyses, Cox proportional hazards model was used to estimate hazard ratio (HR) and 95% confidence interval (CI). Factors associated with progression at $P<0.1$ in univariate analysis would be included in multivariate analysis and mutually adjusted. Further, analysis was stratified by enrollment cytology ("normal cytology" (NILM) versus "mildly abnormal cytology" (ASC-US or LSIL)) and age (<30 years versus ≥30 years) to optimize the application scope of triage markers. SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA) was used. All statistical tests were two-sided. A level of 0.05 was chosen to indicate statistical significance.

3 Results

Two hundred and seventy-three patients, with a mean age of 36.5 years (range 22–62 years) at registration, completed follow-up. Fifty patients (18.3%) were HPV16/18-positive, while 191 cases (70.0%) were preceded by mildly abnormal cytology (ASC-US/LSIL) at enrollment. During the 2-year follow-up, 190 cases (69.6%) regressed, 37 cases (13.6%) persisted, and 46 cases (16.8%) progressed. Among the progression, 37.0% (17/46) occurred at the first follow-up, 30.4% (14/46) at the second, 17.4% (8/46) at the third, and 15.2% (7/46) at the end.

In univariate analysis, age, marital status, reproductive history, contraception, menopausal status, sexual debut, and antecedent cytology were excluded at $P>0.1$ (Table 1). With mutual adjustment, HPV16/18 positivity was confirmed as the independent prognostic marker for progression in the multivariate analysis (Table 1). The 2-year cumulative progression rate was 34.0% (95% CI, 20.9%–47.1%) among HPV16/18 positive patients, while 13.0% (95% CI, 8.6%–17.4%) for HPV16/18 negative patients (Fig. 1a).

To improve the triage strategy, we stratified our analysis by cytology and age at enrollment to examine the risk in subgroups who might be managed with different clinic strategies. When separately stratified, the progressive risk associated with HPV16/18 was not significantly elevated in patients preceded by normal cytology or aged below 30 years (Table 2). Further cross stratification showed that the elevated progressive risk associated with HPV16/18 was only remarkable among cases preceded by mildly abnormal cytology (ASC-US or LSIL) and aged 30 years or older (Table 2). In this subset, the 2-year cumulative progression rate was 50.0% (95% CI, 29.1%–70.9%) among HPV16/18-positive patients, while 14.8% (95% CI, 8.6%–21.0%) for HPV16/18 negative cases (Fig. 1b).

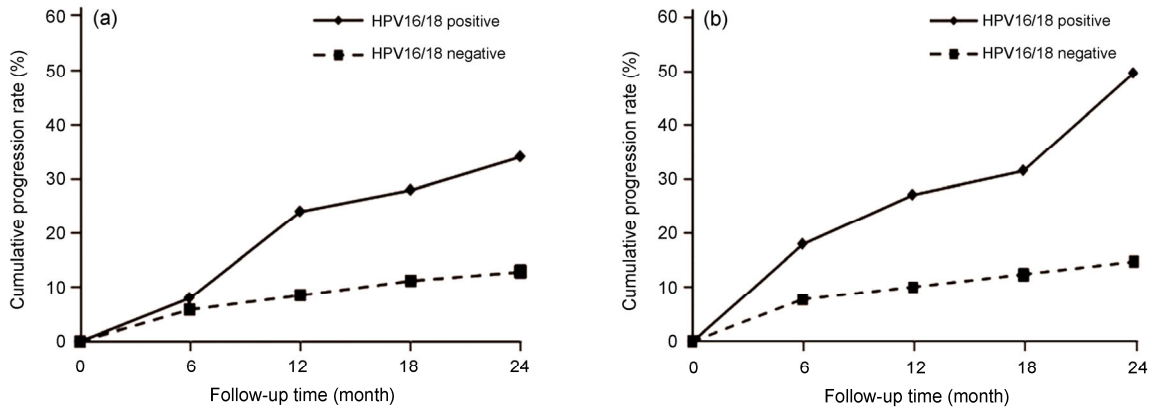

Fig. 1 Cumulative progression rates over 2-year period according to HPV16/18 genotyping at enrollment
(a) All patients (n=273); (b) Patients preceded by ASC-US/LSIL cytology and aged 30 years or older (n=150)

Table 1 Univariate/multivariate analysis of prognostic factors for 2-year cumulative progression rate

Characteristics	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age				
<30 years	Reference			
≥30 years	1.231 (0.574–2.642)	0.594		
Marital status				
Married	Reference			
Single	0.488 (0.118–2.020)	0.322		
Childbearing				
0	Reference			
≥1	2.968 (0.717–12.290)	0.133		
Contraception				
Oral contraceptive	0.474 (0.065–3.473)	0.462		
Condom	0.576 (0.282–1.175)	0.129		
Other	Reference			
Menopausal status				
Premenopause	Reference			
Menopause	0.608 (0.147–2.512)	0.492		
Sexual debut				
<20 years old	1.262 (0.495–3.216)	0.626		
≥20 years old	Reference			
Sexual partner[b]				
1	Reference			
≥2	0.452 (0.190–1.074)	0.072	0.436 (0.183–1.039)	0.061
Enrollment cytology				
NILM	Reference			
ASC-US/LSIL	1.498 (0.743–3.020)	0.259		
HPV genotyping				
HPV16/18 positive	2.777 (1.524–5.059)	0.001	2.708 (1.432–5.121)	0.002
HPV16/18 negative	Reference			

NILM: negative for intraepithelial lesion or malignancy; ASC-US: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HPV: human papillomavirus; HR: hazard ratio; CI: confidence interval. [a] Factors associated with 2-year cumulative progression rate at $P<0.1$ in the univariate analysis were included in the multivariate analysis and mutually adjusted. [b] Refer to the lifetime number of sexual partners

Table 2 HPV16/18 positivity-associated 2-year cumulative progression rate, stratified by cytology and age at enrollment

Stratification	HR (95% CI)	*P*
Cytology		
NILM	2.757 (0.797–9.534)	0.109
ASC-US/LSIL	3.055 (1.527–6.116)	0.002
Age		
<30 years	1.265 (0.255–6.276)	0.774
≥30 years	3.327 (1.733–6.386)	<0.001
Cytology & age		
NILM & <30 years	1.612 (0.099–26.197)	0.737
NILM & ≥30 years	3.650 (0.911–14.627)	0.068
ASC-US/LSIL & <30 years	1.888 (0.220–16.241)	0.563
ASC-US/LSIL & ≥30 years	3.314 (1.575–6.972)	0.002

HPV: human papillomavirus; NILM: negative for intraepithelial lesion or malignancy; ASC-US: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HR: hazard ratio; CI: confidence interval

4 Discussion

To our knowledge, this study is the first to assess the triage value of HPV16/18 genotyping in LSIL/CIN1 preceded by normal or mildly abnormal cytology. Among the four HPV tests approved by the US Food and Drug Administration (FDA), only the Cobas HPV test could genotype HPV16/18 separately. However, when we started our research in June 2012, the Cobas HPV test had not yet been approved by the FDA. In view of the good performance of the HPV GenoArray test in our previous studies (Ye *et al.*, 2010a; 2010b), as well as the excellent concordance with other HPV tests such as Amplicor HPV test and Roche Linear Array (Grisaru *et al.*, 2008; Liu *et al.*, 2010), we adopted the HPV GenoArray test in the current research.

It is well known that HPV infection is the causal agent underlying cervical carcinogenesis (Walboomers *et al.*, 1999). The strong etiological link between HPV infection and cervical cancer has led to the routine application of HPV testing in improving existing cytology-based cervical cancer screening, managing women with equivocal cytology following surgically or ablatively treated cervical lesions, and so on. Compared with HPV testing, HPV genotyping has not been widely applied in clinical practice.

Among HPV genotypes, HPV16 and 18 were considered to have the most potent carcinogenic potential (Dahlström *et al.*, 2010; de Sanjose *et al.*, 2010; Rijkaart *et al.*, 2012; Bzhalava *et al.*, 2013; Tjalma *et al.*, 2013; Wheeler *et al.*, 2014), being associated with about 70% of cervical cancers worldwide (de Sanjose *et al.*, 2010; Li *et al.*, 2011). The powerful carcinogenicity of HPV16/18 made them the most meaningful genotyping targets in clinical practice. In cross-sectional studies, HPV16/18 genotyping stratified HPV-positive women by their risk of prevalent high-grade cervical lesions (Castle *et al.*, 2011; Wright *et al.*, 2011; Lagos *et al.*, 2015; McKenna *et al.*, 2016). It also served as a reliable predictor of residual disease following conization for cervical precancerous lesion (Kang *et al.*, 2016). In prospective studies, HPV16/18 positivity is linked with a higher risk of future high-grade cervical lesions (Khan *et al.*, 2005; Bulk *et al.*, 2007; Persson *et al.*, 2015). Based on evidence in the research literature, ASCCP guidelines recommend that women aged 30 years or older with normal cytology but positive HPV16/18 should be referred for immediate colposcopy, because they are at particularly high risk of current or future high-grade cervical lesions (Massad *et al.*, 2013). In this study, we have confirmed the triage value of HPV16/18 genotyping in LSIL/CIN1, which is comparable and complementary to earlier published data.

In cytology sub-analysis, HPV16/18 genotyping provided little predictive value to LSIL/CIN1 preceded by normal cytology. It is inconsistent with early data, which showed an elevated 10-year risk of high-grade cervical lesions in women with normal cytology but positive HPV16/18 (Khan *et al.*, 2005). However, it is worth noting that this previous research had no baseline data of histodiagnosis (Khan *et al.*, 2005), so could not exclude patients with already existing high-grade cervical lesions at enrollment. Given the high current prevalence of high-grade cervical lesions among HPV16/18-positive women with normal cytology (Wright *et al.*, 2011), the positive follow-up association obtained without baseline histodiagnosis needs further verification. Another possible explanation for our negative relationship between HPV16/18 genotyping and LSIL/CIN1 preceded by normal cytology is low statistical power. Further study with a larger sample size and longer follow-up period is required to test this possibility.

To balance risk versus benefit, we also tailored our strategy by age. Because of maximal exposure but minimal acquired immunity, HPV prevalence is high in young women (Bosch *et al.*, 2008; McKenna and McMenamin, 2014). However, most young women have an effective immune response to clear the acute infection within a short time (Rodriguez *et al.*, 2008). Considering the high spontaneous regression rate among this age group, HPV testing is not recommended (Davey *et al.*, 2014). Similarly, colposcopy associated with HPV16/18 is restricted to women aged 30 years or older (Massad *et al.*, 2013). HPV16/18 genotyping showed no triage value under age of 30 years. Our observation supported the notion that HPV strategy should be age-related. Young women should be managed conservatively, especially for minor abnormalities (Massad *et al.*, 2013).

5 Conclusions

HPV16/18 positivity is predictive of progression for women with LSIL/CIN1 preceded by mildly abnormal cytology, who are aged 30 years or older. Closer follow-up is required for this high-risk subset. For patients at risk of loss-to-follow-up, immediate treatment (including ablative or resectional treatment based on transformation zone type and colposcopy) is a rational recommendation.

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Contributors

Jing YE, Xing XIE, Wei-guo LU, and Xiao-dong CHENG conceived and designed the project. Bei CHENG, Yi-fan CHENG, and Ye-li YAO participated in the recruitment

and follow-up of patients. Jing YE analyzed the data and wrote the manuscript. Xing XIE, Wei-guo LU, and Xiao-dong CHENG revised the manuscript. All authors agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Compliance with ethics guidelines

Jing YE, Bei CHENG, Yi-fan CHENG, Ye-li YAO, Xing XIE, Wei-guo LU, and Xiao-dong CHENG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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中文概要

题　目：人乳头瘤病毒 16/18 分型在细胞学轻度异常的低度宫颈病变中的预测价值

目　的：评估人乳头瘤病毒（HPV）16/18 分型在细胞学正常或轻度异常的低度宫颈病变中的预测价值，为临床分流决策提供依据。

创新点：目前对于细胞学正常或轻度异常的低度宫颈病变患者缺乏有效分流策略。本研究首次探索 HPV16/18 分型对这部分患者疾病转归的预测价值。

方　法：新招募细胞学正常或轻度异常的低度宫颈病变患者，以 6 个月为间隔随访 2 年，采用 Cox 回归模型对入组 HPV16/18 分型结果与疾病转归进行关联分析。

结　论：对于 HPV16/18 阳性，细胞学轻度异常，且 30 岁及以上的低度宫颈病变患者，可以考虑比保守随访更积极的诊疗方案。

关键词：低度鳞状上皮内病变；宫颈上皮内瘤变 1 级；人乳头瘤病毒（HPV）；HPV16/18 分型；预测价值；前瞻性研究