

Research Paper

HPV test results and histological follow-up results of patients with LSIL Cervical Cytology from the Largest CAP-certified laboratory in China

Baowen Zheng^{1*}, Huaitao Yang^{2*}, Zaibo Li³, Guijian Wei¹, Jia You¹, Xiaoman Liang¹, Chengquan Zhao⁴✉

1. Guangzhou Kingmed Diagnostics, Guangzhou, Guangdong 510330, P. R. China;
2. Department of Pathology, University Cincinnati College of Medicine, Cincinnati, OH 45219, USA;
3. Department of Pathology, Wexner Medical Center at Ohio State University, Columbus, OH 43210, USA;
4. Department of Pathology, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA.

* Both authors made equal contributions to this paper.

✉ Corresponding author: Chengquan Zhao, MD, Department of Pathology, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA. Tel: +412-641-6678, Fax: +412-641-1675, Email zhaoc@upmc.edu

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Abstract

Background: Age-adjusted evaluations have explored the possible utility of (HPV test results in women with LSIL Pap. We investigated HPV test results and histopathologic follow-up results of LSIL patients from China's largest CAP-certified laboratory.

Methods: Patients with LSIL between 2011 and 2015 from the Guangzhou Kingmed Diagnostics were retrospectively retrieved and their hrHPV test results and histological follow-up results were collected and analyzed.

Results: LSIL result was identified in 37,895 cases from 2,206,588 Pap tests (1.7%) including 1,513,265 liquid-based cytology and 693,323 conventional Pap tests. The average of these women was 38.4 years (15-88). The LSIL reporting rate in women <30 years was significantly higher than that in women > 30 years (2.1% vs 1.7%). The age specific reporting LSIL rates declined with increased age. 8,014 of 37,895 (21.2%) women with LSIL cytology also had HC2 HPV test results. 75.8% of women with LSIL Pap tests were hrHPV+ and the HPV+ rates declined with increased age except in patients older than 60 years. Overall histopathologic diagnoses within 6 months after LSIL were identified in 5,987 of 37,895 patients at Guangzhou Kingmed Diagnostics. CIN2/3 was identified in 15.2% patients, CIN1 in 66.9%, negative in 14.9% patients. No invasive carcinoma was found in all patients. Of 8014 patients with LSIL Pap test and HPV testing results, 1727 patients had histological follow-up within 6 months after Pap cytology test and HPV testing. The detection rate of CIN2/3 was significantly higher in patients with positive HPV testing result than that in patients with negative HPV testing result (17.8% vs. 8.1%). Among patients with LSIL/HPV negative tests, CIN2/3 was detected in 1 of 30 (3.3%) women aged 50 years and above, appearing lower than those in women less than 50 years (8.0%, 28/351, P=0.357).

Conclusion: This is the largest histological follow-up study in women with LSIL Pap from China and the data are helpful in establishing a baseline for better understanding the status of cervical screening in China. The 85.1% positive predict value of LSIL Pap cytology for follow-up CIN lesion was within currently recognized benchmark ranges.

Key words: cervical cytology, LSIL, HPV, CIN, Cervical cancer, China.

Introduction

Cervical cancer remains an important public health problem in Chinese women, especially among women living in rural China.¹ In contrast to the decreasing incidence trends in developed countries, a

substantial increase in cervical cancer incidence was seen in China and it is estimated that 98,900 new cases and 30,500 mortality cases occurred in 2015.² Most cervical cancer and its precursors are caused by

persistent high-risk Human Papillomavirus (HPV) infection. While opportunistic cervical screening services are now available in urban areas of China, only during the last decade the prevention services been proposed to gradually widen cervical screening access to rural China.³ Currently there is no well-established systematic national cervical cancer registry, no well-organized national cervical screening program,^{1,3} Furthermore, no uniform national standards for cervical cytology quality control exist for laboratories serving this still largely unscreened population. We recently published the Pap cytology reporting profile of China's largest independent laboratory, KingMed Laboratory, which has achieved accreditation through the College of American Pathologists (CAP) and International Laboratory Accreditation Program (LAP), demonstrating that the Bethesda System (TBS) cytology reporting rates from a database of almost 2.37 million Papanicolaou (Pap) test reports were within established CAP benchmark ranges and the histopathologic follow-up cervical intraepithelial neoplasia (CIN) 2+ rates from patients with HSIL cervical cytology results was also within currently recognized benchmark ranges^{4,6}.

In current study, we extend the previous findings from Kingmed Diagnostics to analyze HPV test results and histopathologic follow-up results of patients with low-grade squamous intraepithelial lesion (LSIL) cervical cytology.

Materials and Method

A retrospective study was designed to document LSIL cervical cytology reports from the Guangzhou Kingmed Diagnostics Cytology Laboratory during a period of 5 years from 2011 to 2015. All HPV tests were performed in the CAP accredited Microbiology Laboratory of Kingmed Diagnostics. HPV tests and histological follow-up results were collected and analyzed. Histopathologic tissue procurement procedures included endocervical curettage, cervical biopsy, diagnostic cervical excision by loop electrosurgical excision procedures or cold-knife conization, and hysterectomy.

Four liquid-based cytology (LBC) preparations were used in the KingMed laboratory, including ThinPrep (Hologic, Bedford, Mass), SurePath (BD Diagnostics, Franklin Lakes, NJ), Liqui-PREP (LGM International, Melbourne, FL), and LITUO (Lituo Biotechnology Co., Ltd, Hunan, China). All LBC slides were prepared in the laboratory according to manufacturers' instructions. The Chinese LITUO LBC method is similar to other filtration LBC methods; a sample is fixed in an ethanol based liquid preservative solution and a proprietary filtration method is used for slide preparation. An LTS-YJ2000 automated

system (Lituo Biotechnology Co, Ltd, Hunan, China) is used for slide preparation⁴. Conventional Pap tests (CPT) were collected and fixed by individual clinicians and sent to the laboratory for slide preparation and review. Pap test collection methods were largely decided by clinicians.

All Pap tests were reported using the Bethesda System (TBS) 2001 terminology. In this study TBS LSIL terminology refers only to cytology results. Laboratory workload standards, quality control practices, and cytology-histology correlation reviews were all performed in accordance with current CAP LAP checklists. All Pap test screening and final interpretations were performed by a group of around 30 pathologists specialized in gynecologic cytology in the Kingmed Guangzhou Laboratory^{4,6}. High-risk HPV (hrHPV) test was performed by using the Hybrid Capture 2 (HC2) test (Qiagen, Hilden, Germany).⁷ The source of hospitals that specimens were collected and the description of Kingmed Guangzhou Laboratory cytology personnel was described in our recent publications.⁴⁻⁷

The Pearson chi-square test was used for statistical analysis, which was conducted with SAS 9.1 software (SAS Institute, Cary, NC). A P value less than .05 was considered statistically significant.

Results

During the 5-year retrospective study period, total 2,206,588 gynecologic cytology reports were identified, including 1,513,265 LBC (68.6%) and 693,323 CPTs (31.4%) (Table 1). The average age of these women was 38.4 years (15-88). The case numbers increased gradually during the study period, and the annual number of Pap tests reported in 2015 was 2 times more than that reported in 2011 (590,848 versus 299,615, a 97.2% increase; Table 1).

Table 1. The case number for types of Papanicolaou test by Years.

	ThinPrep	SurePath	LPT	LITUO	CPT	Total
2011	157,320	22,934	25,144	8,360	85,857	299,615
2012	143,157	34,115	25,278	16,961	118,274	337,785
2013	152,821	42,318	25,606	31,213	157,761	409,719
2014	171,353	28,069	0	176,812	192,387	568,621
2015	168,189	31,600	0	252,015	139,044	590,848
Total	792,840	159,036	76,028	485,361	693,323	2,206,588

Abbreviations: ThinPrep, Hologic, Bedford, Massachusetts; SurePath, BD Diagnostics, Franklin Lakes, New Jersey; LPT, Liqui-Prep, LCM International, Melbourne, Florida; LITUO, Lituo Biotechnology Co, Hunan, China; CPT, conventional Papanicolaou test.

The overall LSIL reporting rate was 1.7% (37,895) among 2206,588 cases of Pap tests. The LSIL reporting rate in LBCs was 2.1% (31976/1513265), significantly higher than 0.9% (5919/693323) in CPT ($p < 0.001$). In

LBC groups, SurePath showed the highest LSIL reporting rate (3.3%) while LPT showed the lowest LSIL rate (1.5%). LSIL reporting rate was 2.0% in ThinPrep preparation, significantly lower than 3.3% in SurePath preparation ($P < 0.001$), similar to 2.0% in LITUO preparation ($p = 0.061$), and significantly higher than 1.5% in LPT preparation ($p < 0.001$) (Table 2). LSIL reporting rates with different preparations were within expected ranges for the CAP 2006 survey benchmarks.⁸

Table 2. LSIL reporting rates in different Pap test preparation methods.

Cytology	Total Pap	Average age (range)	LISL No (%)	Average age (range)
ThinPrep	792,840	36.47 (15-83)	16086 (2.0)	38.08 (15-89)
SurePath	159,036	35.99 (16-88)	5171 (3.3)	37.43 (16-80)
LPT	76,028	35.00 (16-77)	1104 (1.5)	37.58 (16-79)
LITUO	485,361	41.49 (15-78)	9615 (2.0)	43.34 (15-84)
CPT	693,323	41.93 (16-78)	5919 (0.9)	44.40 (16-86)
Total	2,206,588	38.43 (15-88)	37895 (1.7)	40.57 (15-89)

Abbreviations: ThinPrep, Hologic, Bedford, Massachusetts; SurePath, BD Diagnostics, Franklin Lakes, New Jersey; LPT, Liqui-Prep, LCM International, Melbourne, Florida; LITUO, Lituo Biotechnology Co, Hunan, China; CPT, conventional Papanicolaou test; LSIL, low-grade squamous intra-epithelial lesion; No, number; Pap test, Papanicolaou test.

Age-specific LSIL reporting rates and HPV-positive rates

The LSIL reporting rates in different age-specific groups were summarized in Table 3. The age specific reporting LSIL rate gradually declined with increased age with the highest report rate 3.6% in group of women younger than 20 years. If the women were divided into two age groups, LSIL report rate was 2.1% (7,419/350,627) in women <30 years, significantly higher than 1.7% (28,373/1,697,087) in women ≥ 30 years ($p < 0.001$). 8,014 of 37,895 (21.2%) women with LSIL cytology also had HC2 HPV test results. A positive hrHPV DNA result was obtained in 6,074 of a total 8,014 (75.8%) women with LSIL Pap tests. The age-stratified hrHPV prevalence analyzed in 10-year intervals and the 95% CI were shown in table 4. The hrHPV positive rate was highest in adolescents (87.5%). There was a clear decline in the hrHPV prevalence in older groups. When women were divided into 2 group groups (younger and older) based on the different cut points of 30, 40 and 50 years, the hrHPV positive rate was significantly higher in all of the younger groups than in the older age groups (<30/ ≥ 30 78.5%/71.4%, $p < 0.001$; <40/ ≥ 40 78.5%/71.4%, $p < 0.001$; <50/ ≥ 50 76.2%/71.0%, $p = 0.004$). HrHPV positive rate appeared higher in women 60 years and older than that in women 50-59 age group, 77.2% vs 69.8%. However, the difference of hrHPV positive rates between these two age groups showed no statistical significance ($p = 0.13$), which may

be caused by the small case numbers in the group of women aged 60 years and above.

Table 3. LSIL reporting rates in different age groups.

Age, years	Total Pap test No	LSIL No	%	95% CI
<20	14,343	517	3.6	3.3-3.9
20-29	336,284	6,902	2.1	2.0-2.1
30-39	656,239	11,346	1.7	1.7-1.8
40-49	705,667	12,651	1.8	1.8-1.8
50-59	265,011	3,542	1.3	1.3-1.4
60-69	62,888	751	1.2	1.1-1.3
≥ 70	7,282	83	1.1	0.9-1.3
Unknown	158,874	2,103	1.3	1.3-1.4
Total	2,206,588	37,895	1.7	1.7-1.7

Abbreviations: LSIL, low-grade squamous intra-epithelial lesion; No, number; Pap test, Papanicolaou test; CI, confidence Interval.

Table 4. HPV positive rates in women with LSIL Pap in different age groups.

Age, years	HPV tested No	HPV positive No	%	95% CI
<20	120	105	87.5	80.2-92.8
20-29	1933	1600	82.8	81.0-84.4
30-39	2653	1989	75.0	73.3-76.6
40-49	2333	1669	71.5	69.7-73.3
50-59	519	362	69.8	65.6-73.7
≥ 60	101	78	77.2	67.9-85.0
Unknown	355	271	76.3	71.6-80.7
Total	8014	6074	75.8	74.8-76.7

Abbreviations: LSIL, low-grade squamous intra-epithelial lesion; No, number; HPV, human papillomavirus; CI, confidence Interval.

Histopathologic follow-up results in women with LSIL cytology

Of 37,895 women with LSIL Pap test results, 5,987 (15.8%) had at least one histopathologic follow-up diagnosis within 6 months after the LSIL Pap test at KingMed laboratory, including 5,342 cases with LBC (89.2%) and 645 cases with CPT (10.8%) (Table 5). The Kingmed Diagnostics is an independent laboratory and cervical cytology and surgical pathology specimens are received from diverse hospitals. Cases with follow-up surgical pathology at the outside institution were excluded from current study. For most patients, the biopsy represented the first histological follow-up result. If there were 2 or more follow-up histologic results, the more serious lesions were recorded. The average age of the patients with histopathologic follow-up results was 38.4 years. Overall, CIN2/3 lesion was identified in 909 (15.2%) patients, including 909 of 5,342 patients (15.3%) with LBC and 93 of 645 patients (14.4%) with CPT, which was not statistically different ($p = 0.095$). CIN1 lesion was found in 66.9% of the patients and negative cases in 14.9% of the patients. No invasive cervical carcinoma diagnoses identified. The CIN2/3 histopathologic follow-up results were compared

with after LSIL Pap tests by using different cytological preparations. CIN2/3 detection rate in ThinPrep was significantly higher than that in SurePath preparation (16.2% vs. 13.1%, $p=0.017$), but was not significantly different when other cytology preparation methods including CPT were compared with individually with ThinPrep result.

Table 5. Histopathologic follow-up results after LSIL cytology with different Pap test methods.

Cytology	F/u case No	CIN2/3 (%)	CIN1 (%)	Negative (%)
ThinPrep	3,066	498 (16.2)	2,139 (69.8)	429 (14.0)
SurePath	994	130 (13.1)	720 (72.4)	144 (14.5)
LPT	155	22 (14.2)	104 (67.1)	29 (18.7)
LITUO	1,127	166 (14.7)	754 (66.9)	207 (18.4)
CPT	645	93 (14.4)	467 (72.4)	85 (13.2)
Total	5,987	909 (15.2)	4,184 (66.9)	894 (14.9)

Abbreviations: LSIL, low-grade squamous intra-epithelial lesion; Pap test, Papanicolaou test; ThinPrep, Hologic, Bedford, Massachusetts; SurePath, BD Diagnostics, Franklin Lakes, New Jersey; LPT, Liqui-Prep, LCM International, Melbourne, Florida; LITUO, Lituo Biotechnology Co, Hunan, China; CPT, conventional Papanicolaou test; F/u, follow-up; No, number; CIN, cervical intraepithelial neoplasia.

Of 8014 patients with LSIL Pap test and HPV testing results, 1727 patients had histological follow-up within 6 months after Pap cytology test and HPV testing. The detailed histopathologic follow-up results, correlated with hrHPV test results and stratified by ages in 10-year age group intervals, are present in table 6. The detection rate of CIN2/3 was significantly higher in patients with positive hrHPV testing compared patients with negative hrHPV testing (17.8% vs. 8.1%, $p<0.001$). The overall CIN detection rate was 88.8% (1185/1334) in women with positive hrHPV testing, significantly higher the rate of 84.7% in women with negative hrHPV testing ($p=0.029$). Regardless hrHPV testing results, CIN2/3 detection rate was 11.4% (54/475) in women age less than 30 years, significant lower than 17.4% (208/1198) in women age 30 years and above ($p=0.002$). In hrHPV negative group CIN2/3 detection was found in 7.9% women (28/351) age less than 50 years, appearing higher 3.3% in women aged 50 years and above.

However the difference showed no statistical significance ($p=0.357$) due to the small case numbers.

Discussion

The Kingmed laboratory is the largest independent laboratory in China with CAP LAP certification and International Organization for Standardization (ISO) certification. As part of an effort to improve patient safety by meeting or exceeding requirements achieve laboratory standardization according to international standards, Kingmed laboratory established a quality assurance program to analyze its cervical cytology reporting rates and histologic follow up results for patients with abnormal Pap cytology. Recently, the TBS reporting rates for 1,394,389 Pap tests between 2007 and 2012 from Kingmed laboratory have been published and were found to be largely within current CAP benchmark ranges.⁴ Furthermore, the recently published data from Kingmed also demonstrate the positive predict value (PPV) for CIN2/3 diagnoses after HSIL cytology reports fall within available CAP benchmark ranges and the cytology-histology correlation rate in patients with SCC cytology reports well falls in the benchmark range from CAP.⁵ Data presented in the current study further extend prior findings by including LSIL reporting rates in different age groups, HPV-positive rates and histological follow up results from KingMed laboratory. Similar to our previous studies, current study demonstrates the LSIL reporting rate fell into the CAP benchmark ranges and the LSIL reporting rate with LBC was significantly higher than that reported with CPT (2.1% VS 0.9%), which are consistent with previous observations documented by US CAP LAP laboratories (the median reporting rate for LSIL in ThinPrep 3.0% vs Conventional 1.3%).⁸ Among the four LBC methods, the LSIL reporting rate is the highest in SurePath (3.3%) and lowest in LPT (1.5%). The different reporting rates can be caused by many factors, such as specimen collection devices and variable populations.

Table 6. Histopathologic follow-up results for women with LSIL/HPV testing results, by different ages.

Age (Years)	hrHPV Positive Cases				hrHPV Negative Cases			
	Follow-up No.	CIN2/3 (%)	CIN1 (%)	Negative (%)	Follow-up No.	CIN2/3 (%)	CIN1 (%)	Negative (%)
<20	24	2 (8.3)	16 (66.7)	6 (25.0)	3	0 (0)	3 (100)	0 (0)
20-29	367	49 (13.4)	284 (77.4)	34 (9.3)	81	3 (3.7)	68 (84.0)	10 (12.3)
30-39	440	92 (20.9)	298 (67.7)	50 (11.4)	135	15 (11.1)	100 (74.1)	20 (14.8)
40-49	379	75 (19.8)	263 (69.4)	41 (10.8)	132	10 (7.6)	102 (77.3)	20 (15.2)
50-59	68	14 (20.6)	46 (67.6)	8 (11.8)	28	1 (3.6)	18 (64.3)	9 (32.1)
≥60	14	1 (7.1)	6 (42.9)	7 (50.0)	2	0 (0)	2 (100)	0 (0)
Unknown	42	5 (11.9)	34 (81.0)	3 (7.1)	12	3 (25.0)	8 (66.7)	1 (8.3)
Total	1,334	238 (17.8)	947 (71.0)	149 (11.2)	393	32 (8.1)	301 (76.6)	60 (15.3)

Abbreviations: LSIL, low-grade squamous intra-epithelial lesion; HPV, human papillomavirus; F/u, follow-up; No, number; CIN, cervical intraepithelial neoplasia.

Our current data also indicated that LSIL reporting rates declined with increased ages, with the peak in women younger than 20 years. Statistical analysis demonstrated the LSIL reporting rate in women <30 years was significantly high than that in women > 30 years, suggesting the highest prevalence of HPV infection in younger women.

In this study cohort, 75.8% (6,074/8,014) women with LSIL Pap tests had positive HC2 HPV testing results. A large meta-analysis of the HPV test positivity rate of women with LSIL showed that the pooled positivity rate was 76%.⁹ The average HPV-positive rate in our cohort is very similar to this pooled rate, slightly lower than the rate reported by ALTS group,¹⁰ or Kaiser Permanente Northern California (KPNC)¹¹, but higher than that from UK ARTISTIC trials.¹² HPV-positive rate of women aged 30 years and older with LSIL cytology parallels to that from ALTS¹³ and falls between the rates reported by Kaiser Permanente¹¹ and the rate reported by UK ARTISTIC trials.¹² The HPV positive rate was higher in young women than that in women of middle age, consistent with the high prevalence of HPV infection in young women. Surprisingly, the HPV positive rate was also higher in women ≥60 years than that in women 40-59 years.

The 85.1% PPV (5093/5987) of LSIL Pap cytology for follow-up CIN lesions reported in current study was within currently recognized benchmark ranges for international cytology laboratories. The overall CIN2+ (CIN2 and above lesions) rate of women with LSIL cytology in Kingmed data (15.18%) is very close to that from KPNC¹¹ and lower than that from ALTS¹⁴ in sub-categorized HPV-positive women with LSIL cytology, but higher than those of UPMC¹⁵ and Yale's studies¹⁶. Furthermore, the CIN2+ age-specific rates of HPV-positive women with LSIL cytology from our current study are similar to those from KPNC in mid-age women (30-49 year women). However, the CIN2+ rate was sustained after age 50 years rather than gradually decreased as reported in Castle's KPNC.^{11, 17} The sustained high CIN2+ rate with increased age in current study is probably due to unscreened patients and/or the heterogeneity of patients. Meanwhile, in HPV-negative women with LSIL cytology, the CIN2+ rate in current study (8.1%) is higher than that reported from UPMC (3.4%),¹⁸ Kaiser Permanente Northern California (4.0%)^{11, 17} and Methodist Hospital of Houston (1.3%, 1/77)¹⁹ By another calculation method, 32 (11.9%) women had negative HPV testing among 270 women with LSIL and histologic diagnosis of CIN2/3. Taken together, these results indicate the limitation of HPV testing in women with LSIL and suggest immediate colposcopy

may be the best follow up management for women with LSIL.

The data presented in current study together with our previous findings from Kingmed not only demonstrate the advantage of LBC in identifying cervical cytology abnormalities, but also provide an opportunity to compare the performance of different LBC methods, including FDA approved methods (ThinPrep and SurePath) and non-FDA-approved methods (LITUO and Liqui-Prep). The highest documented Kingmed reporting rate for LSIL was with SurePath LBC samples, and the lowest reporting rate was with LPT LBC samples, which are similar to our recently published data regarding HSIL reporting rates.⁵ These differences of LSIL reporting rates among different Pap preparations may also be related to the different populations tested, however, specific reason for the differences cannot be determined with certainty due to the samples from numerous hospitals and different populations. Two LBC preparation methods with cheap price from China were used in this study, the LSIL reporting rates from cases prepared by these two methods were similar to that from cases prepared by ThinPrep, confirming their reliability to detect abnormalities.

In summary, this largest histological follow-up study in women with LSIL Pap from China further extends our previously reported findings from a large CAP-certified independent laboratory using diverse cytology methods and demonstrates the LSIL reporting rate, HPV-positive rate, and the PPV for CIN2/3 diagnoses after LSIL cytology fall within available CAP and UK benchmark ranges and are comparable with other international cytology laboratories. Our data also demonstrated a considerably high CIN2/3 rate in women with LSIL and negative HPV testing, suggesting an intermediate colposcopy would be necessary for these women's management and the limitation with HPV testing for the primary screening. Furthermore, current data are helpful in establishing a baseline for better understanding the status of cervical screening in China.

Competing Interests

The authors have declared that no competing interest exists.

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