Atypical Squamous Cells of Undetermined Significance Cervical Cytology Report Rate and Histologic Follow-up Findings From the Largest College of American Pathologists–Certified Laboratory in China

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Context.—Reports for atypical squamous cells of undetermined significance (ASC-US) and histologic findings are rare in China.

Objective.—To analyze the correlation findings of ASC-US cytology with high-risk human papillomavirus (hrHPV) test and histopathologic follow-ups.

Design.—ASC-US cases with hrHPV test and histologic follow-ups between 2011 and 2015 were analyzed at a College of American Pathologists–certified laboratory.

Results.—A total of 2 206 588 Papanicolaou (Pap) tests were performed, including 1 513 265 liquid-based cytology preparations (68.58%), and 693 323 conventional Pap tests (31.42%). The overall ASC-US reporting rate was 3.77% (83 199 of 2 206 588), with the highest in women aged 40 to 49 years. Of 18 574 women with ASC-US Pap and HPV testing, the hrHPV positivity rate was 34.98% (6498 of 18 574) with the highest in women younger than 30 years. A total of 6012 women with ASC-US Pap test findings had histologic follow-ups within 6 months; the overall cervical intraepithelial neoplasia 2 and above (CIN2+) detection rate was 7.87% (473 of 6012). One thousand nine hundred nine women with ASC-US Pap and HPV testing had histologic results. CIN2+ lesion was found in 13.98% (124 of 887) of women with ASC-US Pap/HPV-positive test results, significantly higher than 2.84% (29 of 1022) for women with ASC-US Pap/HPV-negative test results. Cervical squamous cell carcinoma was found in 3.95% (35 of 887) of women with ASC-US/HPV-positive test results.

Conclusions.—This is one of the largest studies to investigate HPV and histologic follow-up findings in women with ASC-US in China. The ASC-US reporting rate, HPV positivity rate, and CIN2+ detection rate were all within the currently recognized benchmark ranges. These findings may contribute to establishing a baseline for better understanding of the status of cervical screening in China.

Cervical cancer remains an important public health problem in Chinese women, especially in women living in rural China.1 While opportunistic cervical screening services are now available in urban areas, it is only during the last decade that prevention services have been proposed to gradually widen cervical screening access to rural China.2 Currently, there is no well-established systematic national cancer registry or organized cervical screening program in China.3,4 Furthermore, no uniform national standards for cervical cytology quality control exist for laboratories serving this still largely unscreened population.

We recently published the cytology reporting profile of China’s largest independent laboratory, the Kingmed Laboratory, which has achieved accreditation through the College of American Pathologists (CAP) International Laboratory Accreditation Program (LAP), and demonstrated that The Bethesda System (TBS) reporting rates from approximately 1 400 000 Papanicolaou (Pap) tests based on TBS were largely within the established CAP benchmark ranges.3,4 Meanwhile, the positive predictive value of high-grade squamous intraepithelial lesion cervical cytology results for follow-up histopathologic cervical intraepithelial neoplasia 2 and above (CIN2+) lesions were also reported within the currently recognized benchmark ranges for cytology laboratories.5 In the current study, we proceeded to analyze and document the atypical squamous cells of undetermined significance (ASC-US) reporting rate together with high-risk human papillomavirus (hrHPV) test results and histopathologic follow-up findings from China’s largest CAP-certified laboratory, in order to provide the baseline information for cervical screening in China.
MATERIALS AND METHODS

A retrospective study was designed to document ASC-US cervical cytology reports at the Guangzhou Kingmed Diagnostics Cytology Laboratory (Guangzhou, Guangdong, China) from 2011–2015. The ASC-US cases with Hybrid Capture 2 (HC2) HPV tests and histologic follow-up results were found. Cases with histopathologic follow-up results diagnosed in the Guangzhou Kingmed Diagnostics Laboratory within 6 months after the Pap results of ASC-US were selected for analysis. Histopathologic tissue procurement procedures included endocervical curettage, cervical biopsy, diagnostic cervical excision by loop electrosurgical excision procedures or cold-knife conization, and hysterectomy.

Four LBC preparations were used: ThinPrep (Hologic, Bedford, Massachusetts), SurePath (BD Diagnostics, Franklin Lakes, New Jersey), Liqui-PREP (LGM International, Melbourne, Florida), and LITUO (Lituo Biotechnology Co, Ltd, Hunan, China). Conventional Pap tests (CPTs) were also introduced in the laboratory in 2009 as a lower-cost alternative to LBC. 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) is used for slide preparation. An LTS-YJ2000 automated system (Lituo Biotechnology) is used for slide preparation. All Pap tests were reported by using the TBS2001 terminology. Laboratory workload standards, quality control practices, and cytology-histology correlation reviews were all performed in accordance with current CAP LAP checklists. All Pap test screenings and final interpretations were performed by a group of approximately 30 pathologists in the Kingmed Guangzhou Laboratory. The hospitals that specimens were collected from and the description of Kingmed Guangzhou Laboratory cytology personnel were reported in our previous publications.

All HPV testing is performed in the CAP-accredited Microbiology Laboratory of Kingmed Diagnostics. HPV was detected by the HC2 test (Qiagen, Hilden, Germany) for 13 high-risk and intermediate-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) performed as described by the manufacturer. HC2 samples were collected by using the HC2 DNA Collection Device (Qiagen) and stored in specimen transport media. The documented reasons for ordering HPV testing varied and most often were not stated. About 25% of patients had HPV testing ordered explicitly as a reflex test after an ASC-US Pap cytology report from this group of patients. Most cervical screening test orders received by Kingmed Diagnostics are either for Pap testing alone or hrHPV testing alone. Currently, orders for Pap and hrHPV cotesting have gradually increased in China. The samples for the hrHPV test were collected and preserved in 2 different vials if both tests were ordered.

Statistical analyses were performed by $\chi^2$ or Fisher exact test for small case numbers by using the SAS 9.1 System (SAS Institute, Cary, North Carolina). P < .05 was considered statistically significant.

RESULTS

ASC-US Reporting Rates

During the 5-year retrospective study period, a total of 2,206,588 gynecologic cytology tests were performed, including 1,513,265 LBC specimens (68.58%) and 693,323 CPTs (31.42%) (Table 1). The average age was 38 years (15–88 years). The test volume increased gradually during the study period, and the annual number of Pap tests reported in 2015 was almost doubled that reported in 2011 (Table 1).

The overall ASC-US reporting rate was 3.77% (83,199 of 2,206,588), with 4.43% (67,038 of 1,512,265) in LBC preparations and 2.33% (16,161 of 693,323) in CPTs. The difference of ASC-US reporting rates between LBC preparations and CPTs was significant ($P < .001$). Among LBC preparations, ASC-US reporting rates were significantly different ($P < .001$), with the highest reporting rate for SurePath (5.63%, 8956 of 159,036) and the lowest for LPT.

Table 1. Case Numbers for Types of Papanicolaou Test by Years

| Year | ThinPrepa | SurePathb | LPT | LITUO | CPT | Total |
|------|-----------|-----------|-----|-------|-----|-------|
| 2011 | 157,320   | 22,934    | 25,144 | 8360  | 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 |

Table 2. ASC-US Reporting Rates by Using Different Preparation Methods

| Preparations | Total Pap Cases | ASC-US, No. (%) | Age, Average (Range), y |
|--------------|----------------|-----------------|-------------------------|
| ThinPrepa    | 792,840        | 32,713 (4.13)   | 35.82 (15–89)           |
| SurePath     | 159,036        | 8956 (5.63)     | 36.51 (15–91)           |
| LPT          | 76,028         | 2921 (3.84)     | 34.60 (14–77)           |
| LITUO        | 485,361        | 16,161 (2.33)   | 43.53 (17–97)           |
| CPT          | 693,323        |                 |                         |
| Total        | 2,206,588      |                 |                         |

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; CPT, conventional Papanicolaou test; LITUO, Lituo Biotechnology Co (Hunan, China); LPT, Liqui-PREP (LCM International, Melbourne, Florida); Pap, Papanicolaou.

a Hologic, Bedford, Massachusetts.
b BD Diagnostics, Franklin Lakes, New Jersey.
(3.84%, 2921 of 76,028) (Table 2). The reporting rates were, in general, within the benchmark ranges from the CAP 2006 survey.5

The age-specific ASC-US reporting rates were analyzed in 3 age groups. The ASC-US reporting rate showed an increasing trend with increasing ages. It was 3.96% (53,975 of 1,361,906) in the age group of 30 to 49 years, significantly higher than the 3.31% (11,618 of 350,627) observed in the age group less than 30 years, and significantly lower than the 4.13% (13,849 of 335,181) in the age group of 50 years and older (P < .001) (Table 3).

**HrHPV Positivity Rates**

Among 83,199 cases of ASC-US, 18,574 (22.33%) had HC2 HPV test results from the Guangzhou Kingmed Laboratory. The overall hrHPV positivity rate was 34.98% (6,498 of 18,574) with the highest in women younger than 20 years (60.47%, 78 of 129), and the hrHPV positivity rates showed a declining trend with increasing age (Table 4).

**Histopathologic Follow-up Findings for Cases With ASC-US Pap Test Results**

Of 83,199 women with a cervical ASC-US Pap test result, 6,012 (7.23%) had at least 1 histopathologic follow-up result in the Guangzhou Kingmed Laboratory within 6 months after an ASC-US Pap test finding was reported. Most patients had a cervical biopsy as their first histologic follow-up. If there was more than 1 follow-up result, the more serious lesion was recorded. Among the 6,012 patients with histopathologic follow-up results, diagnoses of CIN2+ were reported in 473 patients (7.87%), including 37 squamous cell carcinomas (0.62%). Table 5 summarizes follow-up histologic diagnoses after ASC-US Pap test results by using different cytology preparations. At follow-up, CIN2+ detection rate (8.06%, 401 of 4976) after LBC ASC-US Pap test appeared higher than the observed rate of 6.95% (72 of 1,036) after a CPT ASC-US Pap test, but the difference showed no statistical significance (P = .23). Surprisingly, histologic follow-up CIN1 and above (CIN1+) rate was significantly higher for patients with a CPT ASC-US Pap test finding than for those with LBC ASC-US Pap test finding (66.70% [691 of 1,036] versus 58.78% [2,925 of 4,976]; P < .001).

**Histopathologic Follow-up Findings for Cases With ASC-US Pap Test and HPV Test Results**

Among 18,574 patients with ASC-US Pap test and HC2 HPV test results, 1,099 had histopathologic follow-up diagnoses in the Guangzhou Kingmed Laboratory within 6 months after the ASC-US Pap test was reported. CIN2+ lesion was found in 13.98% (124 of 887) of women with ASC-US Pap test/HPV-positive results, significantly higher than the rate of 2.84% for women (29 of 1,022) with ASC-US Pap test/HPV-negative results (P < .001). CIN1 was detected in 62.68% (556 of 887) of women with ASC-US Pap test/HPV-positive test result, significantly higher than the rate of 50.88% (520 of 1,022) for the women with an ASC-US Pap test/HPV-negative test result (P < .001). Thirty-five cases of cervical squamous cell carcinoma were found from 887 women (3.95%) with an ASC-US/HPVpositive test result, while only 1 case (0.10%) was found from 1,022 women with an ASC-US/HPV-negative test result (P < .001). The histologic follow-up results were also analyzed on the basis of the 3 age groups; there was no significant association between the age and the number of women in whom CIN 2+ or CIN 1 was detected in the HPV-positive group or HPV-negative group (Table 6).

**DISCUSSION**

After the first established data from regular questionnaire surveys conducted in 1996 and 1997, the CAP cervicovaginal cytology benchmarks were updated in 2003 and 2008.5 These reported benchmarks were performed in the United States. Although they are largely consistent with the global prevalence of HPV subtypes, there are several distinguishing characteristics that differ from the data obtained from Eastern Asia according to a most comprehensive and

### Table 3. ASC-US Reporting Rates in Different Age Groups

| Age Group, y | Total Pap Test, No. | ASC-US, No. | % |
|--------------|---------------------|-------------|---|
| <30          | 350,627             | 11,618      | 3.31 |
| 30–49        | 1,361,906           | 53,975      | 3.96 |
| ≥50          | 335,181             | 13,849      | 4.13 |
| Unknown      | 158,874             | 3757        | 2.36 |
| Total        | 2,206,588           | 83,199      | 3.77 |

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; Pap, Papanicolaou.

### Table 4. High-Risk Human Papillomavirus (HPV) Test Positivity Rates in Women With ASC-US Papanicolaou Cytology in Different Age Groups

| Age, y | HPV Tested, No. | HPV Positive, No. | % |
|--------|-----------------|-------------------|---|
| <20    | 129             | 78                | 60.47 |
| 20–29  | 3,325           | 1,513             | 45.50 |
| 30–39  | 6,546           | 2,300             | 35.14 |
| 40–49  | 6,208           | 1,818             | 29.28 |
| 50–59  | 1,422           | 434               | 30.52 |
| 60–69  | 218             | 92                | 42.20 |
| ≥70    | 32              | 10                | 31.25 |
| Unknown| 694             | 253               | 36.46 |
| Total  | 18,574          | 6,498             | 34.98 |

Abbreviation: ASC-US, atypical squamous cells of undetermined significance.

### Table 5. Histopathologic Follow-up Results for Women With ASC-US Cytology by Different Papanicolaou Preparation Methods

| Cytology | Case, No. | CIN2/3, No. (%) | CIN1, No. (%) | Negative, No. (%) |
|----------|-----------|-----------------|---------------|-------------------|
| ThinPrepb | 3,089     | 258 (8.35)      | 1,568 (50.76) | 1,263 (40.89)     |
| SurePathc | 629       | 37 (5.98)       | 326 (51.83)   | 266 (42.29)       |
| LPTa      | 209       | 23 (11.00)      | 100 (47.85)   | 86 (41.15)        |
| LITUO     | 1,049     | 83 (7.91)       | 530 (50.52)   | 436 (41.56)       |
| CPTb      | 1,036     | 72 (6.95)       | 619 (59.75)   | 345 (33.30)       |
| Total     | 6,012     | 473 (7.87)      | 3,143 (52.28) | 2,396 (39.85)     |

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; Papanicolaou test; LITUO, Lituo Biotechnology Co (Hunan, China); LPT, Liqui-PREP (LICM International, Melbourne, Florida).

Explanations:
- a Including 37 squamous cell carcinomas.
- b Hologic, Bedford, Massachusetts.
- c BD Diagnostics, Franklin Lakes, New Jersey.
extensive systematic review conducted in China. Furthermore, there is below-baseline information for cervical screening available in China. The current large-scale assessment of 2,206,588 Pap results showed that the ASC-US rates reported from the largest Chinese laboratory, Kingmed, largely fall within this broad benchmark range reported in 2010 from the CAP survey and are parallel to other historical comparison studies after introduction of LBC in the United States and to the data of a subanalysis from the ATHENA study and the National Breast and Cervical Cancer Early Detection Program.

Clinical trials in the US and European system, with quality assurance more tightly controlled, have documented significantly enhanced performance with LBC when compared with conventional cytology. The advantages of LBC have been linked primarily to both enhanced cellular sampling by increased harvesting of cells from Pap collection devices and the interpretive advantage of immediate wet fixation for enhanced cellular detail. Data from our study provide an opportunity to compare the performance of ASC-US reporting rates of LBC methods developed and used in China, such as LITUO and Liquid-PREP, with the US Food and Drug Administration-approved ThinPrep and SurePath methods currently prevailing in the United States. Our results showed that the LITUO LBC method yielded similar sensitivities to those from US LBC methods, based on ASC-US rates reported in this study. This finding provides valuable evidence that these less expensive test platforms can be a cost-effective alternative for developing countries and rural areas.

A large meta-analysis of the HPV test positivity rate of women with ASC-US showed that the pooled HPV positivity rate ranged from 23% to 74%. The CAP national survey results indicate the frequency of reporting HPV positivity for ASC-US cases (median, 38.3%; 110 laboratories), for ASC-US in women aged 30 years and older (median, 30.7%; 43 laboratories), and for ASC-US in women younger than 30 years (median, 51.3%; 32 laboratories). The average hrHPV positivity rate from the current study is within the reported ranges, similar to the data from the Kaiser Permanente Northern California (KPNC) study, but slightly lower than the reported rates of the ASCUS/LSIL Triage Study (ALTS) group. The slight difference from the ALTS study is likely due to the age composition of the studied population. In the current study, the mean ages were between 35 and 41.9 years, while the ALTS study included predominantly younger women (average age, 24.9 years). It is well known that the hrHPV DNA positivity rate is significantly higher in the younger population, and the prevalence declines significantly in older women. When stratified by age, the hrHPV positivity rates of women aged 30 years and older with an ASC-US cytologic finding are parallel to the reported rates from the ALTS, KPNC, and United Kingdom A Randomised Trial In Screening To Improve Cytology (UK ARTISTIC) trials.

The 60.02% (3,616 of 6,012) positive predictive value of ASC-US Pap cytology for follow-up CIN lesions from the largest CAP-accredited laboratory from China was within the currently recognized benchmark ranges for international cytology laboratories. The overall immediate (6 months after the reference ASC-US Pap test) CIN2+ rate (7.87%) of women with ASC-US cytology in the current study is slightly lower than the reported rates from the ALTS, UK ARTISTIC, and New Mexico HPV Pap Registry. One of the possible explanations is the difference of the follow-up interval. In the current study, we assessed the histologic follow-up results within 6 months after the reference ASC-US Pap interpretation. The New Mexico HPV Pap Registry study showed nearly a 15%, 5-year estimated cumulative rate of CIN2+ in HPV+ women with ASC-US. Meanwhile, the ALTS study reported a 2-year cumulative 15.4% rate for detection of CIN2/3 for women with an ASC-US Pap test finding, and the UK ARTISTIC trials defined CIN2+ as the worst histology within 30 months of entry. Another explanation may be the difference in the prevalence of HPV subtypes between the Chinese population and the Western population. It was reported that the attributions of HPV 52 and HPV 58 to CIN and invasive cancer in China were frequently detected and preceded only by HPV 16 and HPV 18, rather than HPV 45.

In the current study, high-grade histologic lesion (CIN2+) was identified in 13.98% of women with an ASC-US Pap cytologic finding and positive HPV test results, which was also within the benchmarks from most large-scale studies including KPNC and ALTS studies. ALTS reported CIN2/3 was found in 203 of 1132 women (17.9%) with HPV positivity and ASC-US at initial colposcopy and directed biopsy. Many studies reported CIN2/3 detection rates were in a range of 5% to 10%. Histologic follow-up diagnoses of invasive cervical carcinoma in 35 of 887 ASC-US/HPV-positive patients (3.95%) were significantly more likely when compared with the incidence of follow-up cervical cancer diagnoses in the US and European studies.
which may indicate an overall lack of routine screening and lack of lesion removal through screening.24–26

In addition, a CIN2/3 lesion was also found in 2.84% (29 of 1022) of women with HPV-negative/ASC-US Pap test results, approximately twice that reported by the UK ARTISTIC study, KPNC data, and Netherland Population Based Screening Study Amsterdam (POBASCAM) study. 19, 21, 27 Compared with hrHPV-negative women with ASC-US, hrHPV-positive women with ASC-US showed a significant increase in the risk of CIN2+ at all ages, strongly supporting the 2012 American Society of Colposcopy and Cervical Pathology guideline of reflex HPV testing for women with ASC-US cytology.

In summary, this is the largest study to investigate HPV positivity rates and histologic follow-up results in Chinese women with an ASC-US Pap cytologic finding. This study extends our previously reported findings from the largest CAP-certified Chinese laboratory, using diverse gynecologic cytology preparation methods. The TBS reporting rates, hrHPV positivity rates, and CIN2 detection rates are within the published CAP and UK benchmark ranges and comparable with the data from other international cytology laboratories. These data may contribute to establishing a baseline for a better understanding of the status of cervical cancer screening in China.

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