



ORIGINAL ARTICLE

Nationwide survey of cervical cytology laboratory practices in China

Xiang Tao, MD, PhD^{a,*}, R. Marshall Austin, MD, PhD^b,
Lingfei Kong, MD^c, Qing Sun, MD, PhD^d, Qinjie Lv, MD^e,
Haimiao Xu, MD^f, Gang Meng, MD, PhD^g, Xianghua Huang, MD, PhD^h,
Min Hao, MD, PhDⁱ, Qiao Zhou, MD^j, Xianrong Zhou, MD^a,
Liantang Wang, MD, PhD^k, Yue Zhang, MD^l, Shuxia Xu, MD^m,
Qingfang Shi, MDⁿ, Qi Zhou, MD^o, Linchuan Guo, MD^p, Sien Zeng, MD^q,
Yulan Wang, MD^r, Jianhua Zhou, MD, PhD^s, Xiu Nie, MD^t,
Lixiang Tian, MD^u, Danhua Shen, MD^v, Zi Lei, MD^w, Yixin Liu, MD^x,
Jinhong Mei, MD^y, Kam Weng Wong, MD^z,
Annie A. Y. Cheung, MD, PhD, FRCPath, FHKAM(Pathology), FIAC^{aa},
Juan Li, MD, PhD^{bb}, Minghua Zhu, MD^{cc}, Chengquan Zhao, MD^{b,**}

^aDepartment of Pathology, Obstetrics & Gynecology Hospital of Fudan University, Shanghai, China

^bDepartment of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

^cDepartment of Pathology, Henan Provincial Hospital, Zhengzhou, China

^dDepartment of Pathology, Shandong Provincial Qianfoshan Hospital, Jinan, China

^eDepartment of Pathology, Shengjing Hospital of China Medical University, Shenyang, China

^fDepartment of Pathology, Zhejiang Cancer Hospital, Hangzhou, China

^gDepartment of Pathology, Anhui Medical University, Hefei, China

^hDepartment of Gynecology, The Second Hospital of Hebei Medical University, Shijiazhuang, China

ⁱDepartment of Obstetrics and Gynecology, The Second Hospital of ShanXi Medical University, Taiyuan, China

^jDepartment of Pathology, West China Hospital, Sichuan University, Chengdu, China

^kDepartment of Pathology, The First Affiliated Hospital, Sun Yat-sun University, Guangzhou, China

^lDepartment of Pathology, Horqin Right Front Banner People's Hospital, Ulanhot, China

^mDepartment of Pathology, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, Fuzhou, China

*Corresponding author: Xiang Tao, MD, PhD; Department of Pathology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, 200011 China.

**Corresponding author: Chengquan Zhao, MD; Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA 16066.
E-mail address: tutufoliage@hotmail.com (X. Tao); zhaoc@upmc.edu (C. Zhao).

ⁿ Department of Pathology, Gansu Provincial Maternity and Child-Care Hospital, Lanzhou, China

^o Department of Gynecological Oncology, Chongqing Cancer Hospital, Chongqing, China

^p Department of Pathology, The First Affiliated Hospital of Soochow University, Suzhou, China

^q Department of Pathology, Affiliated Hospital of Guilin Medical College, Guilin, China

^r Department of Pathology, Xinjiang Military District General Hospital, Urumqi, China

^s Department of Pathology, Xiangya Hospital, Central South University, Changsha, China

^t Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

^u Department of Pathology, Changchun Gynecological and Obstetric Hospital, Changchun, China

^v Department of Pathology, Peking University People's Hospital, Beijing, China

^w Department of Pathology, First Affiliated Hospital of Kunming Medical University, Kunming, China

^x Department of Pathology, Tianjin Central Hospital of Gynecology Obstetrics, Tianjin, China

^y Department of Pathology, The First Affiliated Hospital of Nanchang University, Nanchang, China

^z Department of Obstetrics & Gynecology, Centro Hospitalar Conde de São Januário, Macau SAR, China

^{aa} Department of Pathology, HKU Cervical Cytology Laboratory and HKU-Shenzhen Hospital Cytology Laboratory, The University of Hong Kong, Hong Kong SAR, China

^{bb} Department of Pathology, Jinan Maternity and Child Care Hospital, Shandong, China

^{cc} Department of Pathology, Shanghai Changhai Hospital, Shanghai, China

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Introduction Cervical cancer rates in China remain high, with only limited opportunistic screening in urban centers and large mostly unscreened rural areas. Cervical cytology practices in China have been changing over the last decade with introduction of The Bethesda System reporting terminology, liquid-based cytology (LBC), and programs for cervical cytology screening of underserved rural populations. An effort was undertaken for the first time to collect nationwide data on cervical cytology laboratory practices in China, a possible first step toward increased standardization and potential development of nationwide cytology quality benchmarks.

Materials and methods Data on cervical cytology practices from 1572 laboratories operating in 26 nationwide Provisional Level Administrative Divisions was collected in an online survey approved through the Obstetrics and Gynecology Hospital of Fudan University in Shanghai.

Results Over 90% of cervical cytology laboratories in China now solely use Bethesda System reporting terminology. LBC is now the most commonly utilized form of cervical cytology, with lower-cost Chinese-manufactured LBC formulations used in almost 70% of laboratories. Nationwide, significantly higher abnormal cytology rates were reported with LBC than with the conventional Papanicolaou smear (CPS); however, the CPS remains a useful low-cost alternative as China strives to extend cervical screening to large underserved rural areas.

Conclusions Abnormal cytology rates were not significantly different when different levels of hospitals were compared. The survey identified nationwide opportunities for cytology quality improvement, including low rates of reporting of unsatisfactory cases and low rates for atypical glandular cells.

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Introduction

Cervical screening in China remains largely limited to occasional opportunistic screening in urban centers,¹ with the majority rural population remaining mostly unscreened.² According to recently published data, nearly 100,000 new cervical cancer cases may be diagnosed nationwide each year, with annual mortality estimates of around 30,000.³

Efforts to modernize cervical cytology practices in China have included widespread introduction of The Bethesda

System (TBS) reporting terminology and introduction of liquid-based cytology,⁴ limited development of specialist cytology training programs, and participation of some laboratories in the international College of American Pathologists' Laboratory Accreditation Program.⁵ No organized screening program⁶ currently exists, and there are no recognized national quality standards. Therefore, as a first step toward increased standardization and potential development of nationwide cytology quality benchmarks,^{7,8} efforts were undertaken to survey cervical cytology practices across the country.

Materials and methods

Data recruiting

A questionnaire was designed to collect nationwide data on Chinese cervical cytology laboratory practices across the country. The study was conducted online under regulations approved by the institutional review board of the Obstetrics and Gynecology Hospital of Fudan University in Shanghai. Survey questions included cytology laboratory location (provincial-level administrative division areas), hospital type (hospitals classified as primary, secondary, and tertiary in a progressively larger and more complex 3-tier system), hospital laboratory ownership (government, military, independent, and private), departmental home of cytology laboratory (Pathology, Clinical Laboratory, Gynecology, and Outpatient Laboratory testing), types of cervical cytology utilized (liquid-based cytology or conventional Papanicolaou smears), staining methods for cervical cytology (Papanicolaou stain or hematoxylin and eosin [H&E]), specific liquid-based cytology methods (ThinPrep,⁹ Sure-Path,¹⁰ or Chinese-manufactured liquid-based cytology formulations), and cervical cytology reporting terminology (The Bethesda System¹¹ or the Papanicolaou Class System¹²). One leader from each of the 26 provincial-level administrative division areas included was selected to promote the online survey in their geographic area. Completion of the online surveys began on April 1, 2018, and ended on May 30, 2018.

Data arrangement

TBS reporting rates were calculated to the nearest tenth of a percentage point. TBS reporting rates that were either unclear or judged by the authors to be clearly inaccurate were deleted from the data analysis. Such circumstances included the format as X% to X% in a large range, the sum of percentage obviously not equal to 100%, or the obviously wrong number. Atypical squamous cell/squamous intraepithelial lesion (ASC/SIL) ratios were calculated by one of the authors for laboratories that provided TBS reporting rates for the recognized categories of TBS cytologic abnormalities. Abnormal or “positive” cytology reporting rates included all cytology reports other than those reported as unsatisfactory or negative for intraepithelial lesion or malignancy (NILM). Not every laboratory responded to every question. Total responses to each question in the survey were designated as denominators in the text and as number (n) in tables.

Statistical analysis

Quantitative data were expressed in the form of lower, median, and upper quartiles. Statistical analysis was performed using IBM SPSS 20.0 (IBM SPSS, Chicago, IL).

Differences between 2 groups and more than 2 groups were compared by the Mann-Whitney U test and the Kruskal-Wallis test, respectively. TBS reporting rates were compared between liquid-based cytology (LBC) and conventional Papanicolaou smears (CPS) using the Wilcoxon signed rank test. Categorical data was analyzed using the χ^2 test. Double-tailed *P* values less than 0.05 were considered statistically significant.

Results

A total of 1656 laboratories enrolled in the online survey, and responses from 84 laboratories were excluded because of incorrect or incomplete information. Therefore, data from 1572 laboratories were included in this study. It was estimated that the survey data covered 20% to 70% of labs with Papanicolaou cytology tests in the provinces participating in the survey. Most provincial-level administration divisions surveyed had more than 40 responses. Two tertiary hospitals, one each in the Hong Kong and Macau special administrative districts, were also included. The numbers of responses from the 26 provincial-level administrative divisions surveyed are shown in Fig. 1, and the geographic areas covered are displayed in Fig. 2. The annual cervical cytology volume of the surveyed laboratories is shown in Table 1. Relatively small laboratories reviewing less than 20,000 cervical cytology specimens predominated. Less than 3% of the surveyed laboratories reported reviewing more than 50,000 cervical cytology specimens per year.

The types of laboratories satisfactorily completing the online surveys were as follows: general hospital laboratories 81.6% (1281 of 1570), gynecologic or obstetric hospital laboratories 12.0% (189 of 1570), unclassified laboratories 3.7% (58 of 1570), and independent laboratories 2.7% (42 of 1570). Levels of hospitals completing the surveys were as follows: tertiary hospitals 54.7% (857 of 1565), secondary hospitals 41.1% (643 of 1565), primary hospitals 0.9% (14

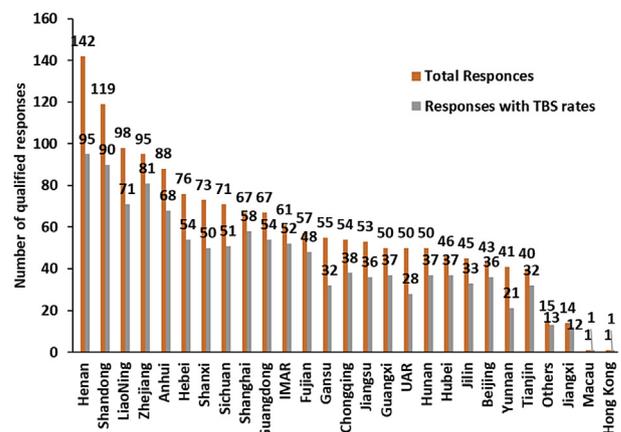


Figure 1 Survey responses from 26 Chinese provincial-level administrative divisions, including inner Mongolian autonomous region (IMAR) and Uyghur autonomous region (UAR).

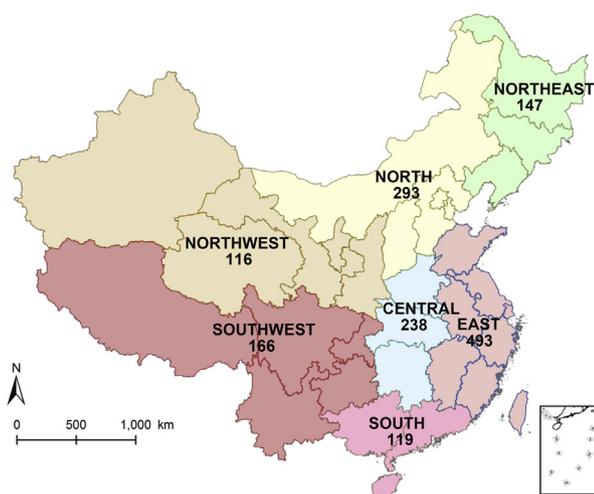


Figure 2 Geographic regions in China participating in nationwide survey. The numbers indicate the total responses for the survey in each region.

of 1565). Ownership of the laboratories was: government-owned hospital laboratories 90% (1415 of 1564), privately owned hospital laboratories 3.6% (57 of 1564), independent laboratories 2.3% (36 of 1564), and military hospital laboratories 2.0% (32 of 1564). In China, cervical cytology was held in one of the following departments: pathology, clinical lab, gynecology, or sending-out for independent labs. The percentage was 90.8% (1419 of 1562), 3.9% (61 of 1562), 2.4% (38 of 1562), and 2.9% (45 of 1562), respectively. This percentage was biased because the distribution of the survey was mainly to pathologists. Cervical cytology staining methods used varied as follows: the largest number of laboratories (61.7%, 912 of 1463) reported using Papanicolaou staining only, followed by 19.5% (279 of 1431) using only H&E staining, and 16.8% (240 of 1431) utilizing both methods. LBC methods used nationwide were led by Chinese-manufactured systems not available in the US in 68.9% (1019 of 1478) of laboratories, followed by ThinPrep in 28.1% (415 of 1478), SurePath in 9.0% (133 of 1478), and “others” in 8.5% (126 of 1478). Most laboratories use only TBS reporting terminology (91.6%, 1363 of 1488),

whereas only 4.0% (60 of 1488) still use only the Papanicolaou class system; 4.4% (65 of 1488) still use both TBS and the traditional Papanicolaou class reporting system (Table 2).

Nationwide reporting rates for TBS categories with different cervical cytology preparation methods are shown in Table 3 for LBC and in Table 4 for CPS. Not all laboratories participating in the survey provided TBS reporting rates: 1150 laboratories provided TBS reporting rates for LBC and 315 provided TBS reporting rates for CPS. Of the 315 laboratories using CPS, 298 of 315 also utilized some LBC.

TBS reporting rates for LBC and CPS were compared utilizing pairwise nonparametric testing (Wilcoxon signed-rank test) to help minimize the impact of differing disease rates between different laboratory facilities. TBS reporting rates are given as percentages of total case volume with the 50th percentile corresponding to the median. The overall median abnormal rate for LBC was 7.5% and 5% for CPS. The difference was statistically significant ($P < 0.01$, Wilcoxon signed-rank test). Squamous cell abnormality rates were consistently higher with LBC than CPS. The median ASC-US rate for LBC was 3.7%, higher than the median ASC-US rate of 2.0% for CPS. The median ASC-H rate for LBC was 0.5% versus 0.2% for CPS. The median LSIL rate for LBC was 1.0% versus 0.5% for CPS. The median HSIL rate for LBC was 0.5% versus 0.1% for CPS. The rates for all abnormal squamous cell categories were significantly higher with LBC than for CPS ($P < 0.01$, Wilcoxon signed-rank test). The atypical glandular cell mean rates were 0.05% for LBC and 0.0% for CPS. Median unsatisfactory rates were 0.2% for both LBC and CPS. The median ASC/SIL ratio was 2.1% for LBC and 2.0% for CPS.

The median abnormal cytology rate did not differ significantly when different types of laboratories were compared: for general hospital laboratories 7.6%, for gynecologic/obstetric hospital laboratories 8.0%, for independent laboratories 6.2%, and also 6.2% for unclassified hospital laboratories (Kruskal-Wallis test $P = 0.460$). Neither ASC-US rates nor ASC/SIL ratios differed significantly among different types of laboratories.

Abnormal cervical cytology rates are shown in Table 5 from different levels of hospitals. The Kruskal-Wallis test with post hoc pairwise testing indicated that abnormality rates vary significantly between the different hospital levels, with a relatively high percentage in primary or secondary levels ($P = 0.040$). Neither were there significant differences for ASC-US rates and ASC-US/SIL ratios compared between tertiary, secondary, and primary hospitals ($P = 0.383$, $P = 0.839$, respectively).

Table 6 shows abnormal cervical cytology rates in 7 geographic regions of the country. The Kruskal-Wallis test with post hoc pairwise testing indicated that abnormal cytology rates were relatively low in southwest, east, and south China and relatively high in central, north, northeast, and northwest China. The ASC-US rate was lowest in east

Table 1 Annual cervical cytology volume in surveyed Chinese laboratories.

Annual cases	Number of papanicolaou tests	
	LBC (%)	CPS (%)
<1000	180 (12.5)	279 (41.2)
1000-4999	583 (40.5)	245 (36.1)
5000-9999	296 (20.6)	76 (11.2)
10,000-19,999	203 (14.1)	44 (6.5)
20,000-49,999	135 (9.4)	19 (2.8)
>50,000	43 (2.9)	15 (2.2)

Abbreviations: LBC, liquid-based cytology; CPS, conventional Papanicolaou smears.

Table 2 Chinese cervical cytology laboratory practices: survey content.

Category	Categorical name	Number	Percentage (%)
Laboratory type (n = 1570)	General Hospital	1281	81.6
	Gynecologic Hospital	189	12.0
	Unclassified	58	3.7
	Independent Lab	42	2.7
Level of hospital (n = 1565)	Tertiary	857	54.7
	Secondary	643	41.1
	Primary	14	0.9
	Unclassified	51	3.3
Hospital ownership (n = 1564)	Government	1415	90.5
	Private	57	3.6
	Independent	36	2.3
	Military	32	2.0
	Others	23	1.5
Departmental home (n = 1562)	Pathology	1419	90.8
	Clinical lab	61	3.9
	Sending-out	45	2.9
	Gynecology	38	2.4
Staining (n = 1431)	Papanicolaou only	912	61.7
	H&E only	279	19.5
	Both	240	16.8
LBC preparations (n = 1478)	Chinese-manufactured	1019	68.9
	ThinPrep	415	28.1
	SurePath	133	9.0
	Others	126	8.5
Reporting system (n = 1488)	TBS	1363	91.6
	Papanicolaou class	60	4.0
	Both	65	4.4

Abbreviations: LBC, liquid-based cytology; TBS, The Bethesda System. ThinPrep (Hologic, Bedford, MA); SurePath (BD Diagnostics, Franklin Lakes, NJ).

China with statistical significance ($P < 0.001$); ASC-US/SIL ratios did not differ significantly between the 7 regions.

Discussion

Cervical cytology screening practices have been changing significantly in China. Two of the most dramatic areas of

change over the last decade that are reflected in our nationwide survey results are the widespread Chinese adoption of TBS reporting terminology and the widespread introduction of LBC. In our survey, over 90% of cytology laboratories now indicate that they are only using TBS reporting (Table 2). Fewer than 5% are still only using the traditional Papanicolaou Class system. In some locations such as Shanghai, conversion to TBS reporting was

Table 3 TBS reporting rates in China for liquid-based cytology preparations (n = 1150).

Category	n	Percentile						
		5	10	25	50	75	90	95
NILM	1150	69.0	76.9	86.3	92.5	95.5	97.7	98.5
ASC-US	1150	0.5	1.0	2.0	3.7	6.0	10.0	14.3
ASC-H	1148	0.0	0.0	0.2	0.5	1.0	3.0	5.0
LSIL	1150	0.0	0.1	0.5	1.0	2.3	5.0	6.4
HSIL	1150	0.0	0.0	0.2	0.5	1.0	2.0	3.5
AGC	1147	0.0	0.0	0.0	0.05	0.2	1.0	1.0
Malignancy	1148	0.0	0.0	0.0	0.0	0.2	1.0	1.8
ASC/SIL	1093	0.5	0.8	1.3	2.1	3.6	7.4	12.0
Unsatisfactory	1148	0.0	0.0	0.0	0.2	1.0	3.0	5.0

Abbreviations: TBS, The Bethesda System; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cell, cannot exclude high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion; AGC, atypical glandular cells; ASC, atypical squamous cells; SIL, squamous intraepithelial lesion.

Table 4 TBS reporting rates in China for conventional papanicolaou smears (n = 315).

Category	n	Percentile						
		5	10	25	50	75	90	95
NILM	315	60.0	75.1	89.0	95.0	98.1	99.4	100.0
ASC-US	315	0.0	0.0	0.6	2.0	4.0	8.0	12.1
ASC-H	314	0.0	0.0	0.0	0.2	1.0	2.0	3.1
LSIL	315	0.0	0.0	0.0	0.5	1.2	3.0	5.0
HSIL	315	0.0	0.0	0.0	0.1	0.6	1.5	2.2
AGC	314	0.0	0.0	0.0	0.0	0.1	0.5	1.0
Malignancy	313	0.0	0.0	0.0	0.0	0.1	1.0	2.0
ASC/SIL	249	0.2	0.6	1.0	2.0	3.9	8.0	10.9
Unsatisfactory	314	0.0	0.0	0.0	0.2	2.0	9.5	15.0

Abbreviations: TBS, The Bethesda System; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cell, cannot exclude high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion; AGC, atypical glandular cells; ASC, atypical squamous cells; SIL, squamous intraepithelial lesion.

prompted by local regulations.⁴ Despite absence of national standards, TBS reporting appears to be well on its way to becoming a de facto national standard. LBC, which has gradually replaced the conventional Papanicolaou smear in Europe and North America, has now also been widely adopted in China as the main form of cervical cytology utilized (Tables 4 and 5). In China, however, lower-cost Chinese-manufactured LBC formulations are now the most commonly utilized form of LBC, in almost 70% of laboratories surveyed (Table 2). US Food and Drug Administration (FDA)-approved LBC formulations are now used in only 37.1% (548 of 1478) of surveyed Chinese cytology laboratories. Limited data have been reported comparing results achievable with the newer Chinese-manufactured LBC formulations compared with US FDA-approved formulations.⁵

Over the last decade, important efforts have been made to begin to introduce cervical cytology screening into the vast rural areas in China where the majority of the population resides and where current estimates indicate that cervical cancer incidence and mortality rates are high.¹³⁻¹⁷ Beginning in 2009, a free government-sponsored National Cervical Screening Program in Rural Areas was begun in over 200 counties, including every provincial-level administrative division.¹⁸ From 2009 to 2011, over 11 million rural

women received this free service, which now targets women of ages 35 to 64 years. By design, the pilot counties were concentrated in China's less-developed central and western regions. Our survey reflects laboratory results from all parts of the country. Use of low-cost CPS has been one approach used to try to reach these underserved populations.² Although significantly higher abnormal rates were reported in our survey with LBC than with CPS (Tables 3 and 4) and have been similarly reported in many other studies,^{19,20} it should always be remembered that it was long-term observational studies utilizing the CPS method that first led to lowering of cervical cancer incidence in many countries around the world.²¹ The impact of the CPS established cervical screening as the first A-rated cancer screening test formally recognized by the United States Preventive Services Task Force.²²

Bivalent and quadrivalent human papillomavirus (HPV) vaccines have only recently been approved by the Chinese FDA.²³ The delayed introduction of the HPV vaccine in China and the absence of either an organized national vaccination program or an organized cervical screening program will continue to buttress the need for traditional cervical screening in China in the years ahead. HPV testing, now widely used in Chinese laboratories,²⁴ was not the focus of our survey. Nevertheless, very high HPV-positive

Table 5 Positive/abnormal rates, ASC-US rates, and ASC/SIL ratios reported by cytology laboratories in different levels of Chinese hospitals.

Level	Positive rate	ASC-US rate	ASC/SIL
Tertiary (n = 670)	6.2 (3.8, 10.4)	3.5 (2.0, 5.7)	2.1 (1.3, 3.6)
Secondary (n = 436)	7.6 (4.0, 13.6)	4.0 (2.0, 7.0)	2.0 (1.2, 3.7)
Primary (n = 7)	8.0 (5.1, 20)	3.9 (2.0, 12.0)	1.3 (0.8, 10.0)
Unclassified (n = 29)	6.1 (4.2, 7.5)	3.7 (2.3, 4.8)	2.0 (1.6, 2.8)
Kruskal-Wallis test	P = 0.040	P = 0.383	P = 0.839

Abbreviations: TBS, The Bethesda System; ASC-US, atypical squamous cells of undetermined significance; ASC, atypical squamous cells; SIL, squamous intraepithelial lesion. "n = X" indicated the number of the responses.

Table 6 Positive/abnormal rates, ASC-US rates, and ASC/SIL ratios reported by cytology laboratories in different geographic regions of China.

Region	Positive rate	ASC-US rate	ASC:SIL
East (n = 388)	5.9 (3.5, 9.5) ^{a,c}	3.1 (1.9, 5.0) ^{d,e}	2.0 (1.4, 3.2)
North (n = 220)	7.4 (4.0, 14.5) ^c	4.3 (2.3, 7.2) ^d	2.2 (1.3, 4.4) ^f
Central (n = 168)	9.0 (4.3, 16.7) ^{a,b}	5.0 (2.4, 8.0)	2.1 (1.2, 4.0)
Southwest (n = 108)	5.3 (3.2, 11.4) ^b	3.0 (1.6, 5.2)	2.4 (1.5, 4.4) ^g
Northeast (n = 101)	7.3 (4.5, 14.2)	4.0 (2.6, 8.0)	2.3 (1.3, 4.3) ^h
South (n = 93)	6.2 (3.8, 9.6)	3.2 (1.8, 5.4)	1.7 (1.0, 2.5) ^{f,g,h}
Northwest (n = 64)	7.3 (3.8, 14.8)	4.9 (1.2, 6.9) ^e	2.1 (1.3, 3.9)
Kruskal-Wallis test	$P < 0.001$	$P < 0.001$	$P = 0.019$

Abbreviations: TBS, The Bethesda System; ASC-US, atypical squamous cells of undetermined significance; ASC, atypical squamous cells; SIL, squamous intraepithelial lesion.

Post hoc test of Kruskal-Wallis showing difference between groups with same letters (^a $P < 0.001$, ^b $P = 0.018$, ^c $P = 0.038$, ^d $P = 0.004$, ^e $P = 0.003$, ^f $P = 0.029$, ^g $P = 0.028$, ^h $P = 0.030$). "n = X" indicated the number of the responses.

rates have been reported in China, around 20% in both younger and older age groups, which could limit the utility of HPV screening in China. High HPV-positive rates and high prevalence of HSIL in older women appear to reflect the limited extent of routine cervical screening and the resulting limited ablation of persistent high grade intraepithelial lesions in the general population.¹

Our survey results also highlight several potential nationwide opportunities for quality improvement. Very low unsatisfactory rates documented in the survey have been previously noted in other analyses of cytology performance in specific Chinese laboratories.^{2,4,5} The very low unsatisfactory rates appear to reflect widespread reluctance on the part of the Chinese laboratories to report unsatisfactory results to client physicians. This issue deserves further interdisciplinary discussion and study by Chinese professionals. Low rates for atypical glandular cells has also been previously noted in several laboratories.^{2,4,5,25} These issues represent opportunities for continuing education efforts nationwide. Another interesting finding in our survey was the use of H&E staining for cervical cytology specimens in almost 20% of laboratories (Table 2). The Papanicolaou stain was painstakingly refined over many years by Papanicolaou himself to enhance cytologic evaluation.²⁶ Results reported in laboratories utilizing H&E staining, however, were similar to results in laboratories using traditional Papanicolaou staining (results not shown). This comparison deserves further study. These nationwide survey results are the first ever assembled in China. This data set could form a foundation for efforts to identify nationwide benchmarks for cytology reporting, similar to those utilized by the College of American Pathologists in its Laboratory Accreditation Program.⁷ The gathering of nationwide data on cytology reporting practices could be a first step towards standardizing cytology practices.⁸

Shortages of qualified health personnel remain a significant barrier to delivering health services to many patients in China, especially in rural areas. There is still no formally recognized cytotechnology profession in the country to help

facilitate more widespread cervical screening. Screening is currently performed by physician specialists who are primarily trained on-the-job in laboratories.⁵ Neither have formal postgraduate fellowship training programs in cytopathology yet emerged. The Chinese Society of Colposcopy and Cervical Pathology founded in 2015, has recently emerged as an important national nonprofit society that promotes cervical screening and cervical cancer prevention in China through educational programs on colposcopy and cervical cytology testing. More than 40 cervical cytology training courses have been held each year with more than 2000 participants from all parts of the country.

Disclosure

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